National Institutes of Health

U.S. DEPARTMENT OF
HEALTH AND
HUMAN SERVICES

Public Health Service
National Institutes
of Health

Research Plan

December 1981

Including

PROCEEDINGS OF THE
ADVISORY COMMITTEE TO THE DIRECTOR

on

Costs of Biomedical Research
and
Government-Industry Research Relationships

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

MEMORANDUM TO: Members of NIH National Advisory Councils and Boards, and Scientific Review Groups

SUBJECT: NIH Research Plan, FY 1983-85

Enclosed for your information is the NIH Research Plan, FY 1983-85. It is derived from a set of structured meetings of the NIH Director with the Institute Directors--established to enhance and integrate planning, budget, and legislative activities in anticipation of Appropriations Committee hearings and the development of the Department's budget requests for FY 1983.

This Research Plan for FY 1983-85 continues the emphasis on approaches to stabilizing support for research project grants and to assessing the impact of this stabilization on other aspects of the NIH program--clinical trials, research centers, R&D contracts, research training, and intramural research.

The proceedings of the Advisory Committee to the Director, NIH, are included as a supplement. As an adjunct to the NIH planning effort, the Committee has continued its examination of relationships among Government, universities, and industry. The supplement documents the Committee's assessment aimed at ensuring continued strength in the research capacity of the academic partners while attaining appropriate accountability in the use of public funds for science without an excessive burden of accounting. The Committee has also explored ways of enhancing cooperative research relationships with industry. These activities have resulted in two reports, with recommendations, for consideration by NIH. As a consequence, NIH will explore an array of potential changes in the system of research support and means of strengthening NIH-industry relationships. These matters will be under intensive review in the next fiscal year.

This Plan and supplement reflect the intense activity within the Department, the Public Health Service, and NIH directed toward husbanding resources for health research in a time of economic austerity. As Dr. Edward Brandt Jr., Assistant Secretary for Health, stated in the keynote address at the meeting of the Advisory Committee to the Director, NIH, on October 1, 1981 (see supplement), the Federal role is especially important in basic research, but it cannot be an exclusive role. There must be a reasonable relationship with industry and with voluntary associations. Dr. Brandt has laid out an agenda on how to set priorities with constrained funds, and these are the issues that will need to be addressed as we begin planning for FY 1984. In particular, NIH will have to examine closely its projected support of research project grants and trainees, and the approximate mix among other program elements.

This Research Plan provides a point of departure for a consideration of these matters. As Dr. Brandt noted in his remarks, it is essential that the entire scientific community participate in these strategies to assure the highest quality programs for the Nation.

This planning document was developed under the direction of Dr. Joseph G. Perpich, Associate Director for Program Planning and Evaluation. Additional copies may be obtained from the Office of Program Planning and Evaluation, Building 1, Room 137, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205, (301) 496-3152.

Thomas E. Malone

Thomas E. Malone, Ph.D.
Acting Director

Attachments

NATIONAL INSTITUTES OF HEALTH
RESEARCH PLAN
FISCAL YEARS 1983-1985

Including

Proceedings of the Advisory Committee to the Director

on

Costs of Biomedical Research and Government-Industry Research Relationships

42d, 43d, and 44th Meetings
of the
Advisory Committee to the Director, NIH
March 16-17, June 8-9, and October 1-2, 1981

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Public Health Service   National Institutes of Health

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FOREWORD

This NIH Research Plan is an outgrowth of enhanced planning and evaluation processes at the National Institutes of Health. Formal planning activities began in the 1960s, and requirements for documentation were added about 1970. Research Plans have been developed since then, but the one represented here and its three predecessors are derived from improved processes that characterize planning efforts for FY 1980-82, 1981-83, 1982-84, and 1983-85. Perspective on current planning processes is afforded by briefly reviewing the nature of planning efforts and the specific problems that confronted NIH planning for the years noted above.

The Research Plan for 1980-82

The NIH Research Plan for 1980-82 reflects a continuing evolution of planning process and substantive issues. The planning process was begun earlier in the year and provided with more structure. One important innovation was the development of a new approach to characterize the research continuum. This derived in particular from a high administration priority for basic research. The SATT approach--Science base, Applications, technology Transfer, and Training--was adopted, and the review of Institute research programs was conducted within this common framework. Thus, activities and issues could be viewed in relation to the course of knowledge development. "SATT" provided a research spectrum against which the general flow and direction of NIH activities could be described.

The Research Plan for 1981-83

The Plan responds in part to the challenge posed by former HEW Secretary Califano to develop health research principles and a five-year plan for health research activities in the Department. A major focus was the stabilization of the Science Base--principally investigator-initiated research project grants. The thrust of the reviews embodied in this Plan is the allocation of resources of each of the Institutes according to the four SATT categories.

The Research Plan for 1982-84

This Plan concentrates on examining ways to stabilize support for research project grants, on involving a broader segment of the research community in the NIH planning process, and on continuing to develop a strategy and plan for support of the Department's health research activities. The proceedings of the Advisory Committee to the Director, NIH, were included for the first time as a supplement. As an adjunct of the NIH planning effort, the Committee has examined a number of cost and accountability issues as these affect the academic science sector.

The Research Plan for 1983-85

This is an outgrowth of the revised NIH planning process, which provides a systematic structure for consideration of strategies and issues. (The major elements of this process are described in Section One of this report.)

The NIH research planning processes are integrated at all points throughout the 12-month planning period. This integration provides NIH with a firmer planning base, a more realistic context in which to consider future directions, and a structure more conducive to making decisions concerning research opportunities. It also furthers development of the agency's preliminary budget submission as a logical followthrough in the planning process.

With the resignation of Dr. Donald S. Fredrickson, Director, NIH, on July 1, 1981, the program reviews, which are held in the summer/fall months as part of the planning process, were cancelled for this fiscal year. But the program performance summaries prepared for those reviews are published here for the first time. These provide descriptions of selected Institute programs and should be useful for a variety of purposes, including fulfillment of certain Departmental requirements in relation to evaluation planning. They will be linked to the regular program reviews and published in the future as part of the NIH Research Plan. It is hoped that over the next three to five years, all major programs will be summarized.

The proceedings of the Director's Advisory Committee during 1981 appear as a supplement to this Research Plan. These focus on two very important emerging issues that face health research planning: (1) building cooperative research relationships with industry, and (2) examining the status of the Government-university relationship in science. Special reports of two working groups of the Committee, published under separate cover, are available from the Office of Program Planning and Evaluation, OD.

This Research Plan for FY 1983-85 and the NIH Evaluation Plan for FY 1982 provide a framework for general consideration of NIH policy, program, evaluation, budget, and legislative concerns. They should prove useful to those interested in the NIH program and mission and future research directions in the 1980s. The addition of program performance summaries to the NIH planning document provides a bridge to the Evaluation Plan for NIH. During the next fiscal year, efforts to seek closer integration of planning, budgeting, evaluation, and legislative processes will continue.

Joseph G Perpich

Joseph G. Perpich, M.D., J.D.
Associate Director for
Program Planning and Evaluation

November 30, 1981
National Institutes of Health

DIRECTOR'S PREFACE

The National Institutes of Health is the principal biomedical research agency of the Federal Government. The purpose of its research is to prevent disease and premature death and to assure everyone the maximum opportunity for freedom from pain and disability. It is a vast and diverse effort, ranging from fundamental research into life processes, health, and disease to the testing and assessment of new clinical applications and the dissemination of results to those who can use them. Biomedical research builds the knowledge base for medical care, health promotion, and disease prevention measures. It also holds the key to containing the rising cost of health care. Such research has had profound effects on mortality and life expectancy over the past century. There is evidence to support the conclusion that the investment in health research yields a high return in the control of loss of productivity and income.

Challenge for the 1980s

Never has there been a comparable period of growth in the knowledge of living things. We are coming closer than ever before to understanding the life processes in cells and tissues, and there is a high degree of confidence that the underlying mechanisms of disease are now becoming approachable because of these insights. This confidence reflects far more sophistication in our knowledge of biology than has ever before been available. Recombinant DNA and hybridoma technologies are but two examples of recent progress. Our ignorance is still vast, but we are on the threshold of some profound transformations in the health sciences.

This is also a period of intensive examination of the investments that our Nation can make for the common good. The demand for fiscal constraints as the cornerstone of efforts to begin the economic healing process will touch all ventures underwritten by the American people. The investment in biomedical research will face increasingly hard scrutiny as the new administration continues to develop approaches to strengthen our economy.

Thus, the challenge of the 1980s will be to sustain the momentum of the revolution in health research while sharing in the constraints required of all sectors. Only with careful stewardship can the enterprise be kept healthy and the stresses be contained. Reasonable balance among program parts will continue to be an imperative, even as total resources are scaled down. Objectives will include--

- Selective growth in areas of high scientific opportunity and persistent activity in those areas in which the need for knowledge is still great;
- Both highly categorical programming and the provision of essential resources with broader institutional support;
- Continuing quality control by competitive review as well as longer-term investments for scientists of proven productivity;
- Continuing support to all component sectors of the biomedical research spectrum, from the most fundamental to the most practical; and finally,
- The drawing into the system of the next generation of researchers.

But the highest NIH priority must be to ensure a predictable level of support for the best research ideas, as judged by scientific peers.

Stability

The most important biomedical discoveries will continue to be made by investigators pursuing their own ideas, and for them to stay in the system, they must produce in a highly competitive situation. This investigator-initiated research is typically supported by the research project grant, which is a commitment to support one or more scientists for a period now averaging three and one-half years. Annually, NIH meets these multiyear commitments first, then new proposals and those requesting renewal compete for remaining project grant funds. The number of such competing awards that NIH has been able to make each year has been subject to considerable change, so that the likelihood of meritorious projects being funded increases or decreases erratically from one year to the next, thereby causing much instability in the conduct of biomedical research.

Both the executive and legislative branches have, in recent years, supported the principle of stabilizing the number of competing awards to be made each year. The new administration has reaffirmed this approach. This will go far in assuring the health of the enterprise during difficult years, and should provide continued ability to pursue areas where research opportunity is most promising, as well as those in which ideas must be stimulated. The extent to which the NIH has been successful in achieving this equilibrium will be examined during the coming year.

This search for stability, however, creates certain tensions as the limits on the amounts available for other activities become more strict. Much consideration has been given in this year's planning process to the impact of the stabilization initiative on clinical trials, research centers, research and development contracts, research training, and intramural research. The share of support going to these activities has declined as investigator-initiated research has been stabilized. It is becoming clear that further proportional reductions cannot be taken without major risk to the vitality of the enterprise as a whole. Thus, actual stabilization levels will probably need some year-to-year adjustments to prevent such an outcome.

One result of this strategy has been to highlight the interdependence of scientific discovery and the maintenance of a pool of well-trained investigators. There is a close and reciprocal relationship between the continued productivity of research and the availability and renewal of the supply of investigators. There has been a steady erosion over the last eight years in the number of trainees supported by NIH. It is now essential to plan support for a minimum number of trainees needed to replenish and sustain the current pool of investigators. We must also seek remedies to the decline in the number of physicians seeking postdoctoral research training. The reasons for this decline are complex, and full solutions through internal adjustments alone may not be possible; but every effort must be made to deal with this difficult problem if our ability to conduct clinical research is to remain vigorous.

Another outcome of this strategy has been the recognition of the important balance between the categorical programs of NIH and the support of what can be called shared resources. These resources are diverse in size and nature, including, for example, centers, which underpin the opportunity for clinical research; the programs of the National Library of Medicine; special repositories for specimens, culture collections, and genetic strains that link the past to the present and provide a base for the future; and special data banks, which serve many different research programs. Because these resources are essential to maintaining the unity of the biomedical research effort, they cannot be ignored during periods of constraint without serious, long-term consequences for the entire enterprise. Because all investigators are served by these resources, the NIH will experiment in the coming years with obtaining broader input on plans and priorities in this area.

Policy Considerations

There are a number of initiatives under way that should help to fine-tune our understanding of existing stresses in the research system and ultimately to enhance our ability to manage through the years ahead. Some of these initiatives are described below.

Indirect Costs

The rising indirect cost rate on research grants, coupled with essentially level budgets, has contributed to a decline in the base of funds available for direct support of research. Perceptions of the nature, causes, and magnitude of the problem vary widely among affected parties; and recent studies, including revised reporting guidelines by the Office of Management and Budget, have led to extensive debate. While the Government recognizes indirect costs as real costs of conducting research for which institutions must be reimbursed, the range of rates charged and their unpredictable but always upward growth are causes of much concern. At the same time, many science faculty at reporting institutions tend to view indirect cost increases as eroding the funds available to support their research.

Director's Preface

During the past year the NIH, through the activities of the Director's Advisory Committee, has brought all divergent interests together in an effort to understand better the anatomy of indirect costs and to see if some improvements are possible in the way business is done. This is an area not lacking in reports, studies, recommendations, and position papers. This issue, however, has remained intractable despite this wealth of examination. We now hope to elicit proposals for some modest experiments that could provide relief to the universities from certain burdensome accounting procedures, broader agreement that accountability issues are being handled equitably, and greater predictability to NIH in the planning and execution of award levels.

Private Sector Research Efforts

It is generally agreed that if the Federal Government were to withdraw support from all worthwhile biomedical research, private sources would not come forth with sufficient funds to keep the effort moving ahead. It is also generally agreed that the private sector has and will continue to play an important role in adapting the discoveries of research to more effective medical practice. There are many recent examples of the cooperative partnership among government, universities, and the private sector which assists in bringing new knowledge into application. Through the Director's Advisory Committee, NIH is taking a hard look at these relationships, with special attention to identifying obstacles to a more active partnership. It may be reasonable and possible to suggest modification of some of the body of rules that tend to limit options here.

NIH Planning Process

The NIH planning process is described in some detail in a subsequent section of this plan. It deserves mention here, for this process has changed with the times to provide a systematic structure in which these strategies and issues can be carefully considered each year. Yet the process is based on a flexibility that allows the type of creative debate and input so essential to the decisions that must be made. It takes on an increasingly significant role as resource questions become more complex.

DS Fredrickson

Donald S. Fredrickson, M.D.
Director
National Institutes of Health

Section One

PLANNING AT THE NATIONAL INSTITUTES OF HEALTH

Introduction

Planning at NIH is a structured and integral part of the development and conduct of health research programs. The planning function establishes the framework through which goals, objectives, and research strategies are assessed, priorities set, resource allocations made, new programs developed and implemented, and existing programs modified.

Each Institute has established its own planning process--and each responds to a common NIH process. These processes are designed to increase the probability that significant knowledge will be produced under a wide range of circumstances and will lead to safe and effective interventions in man. Underlying the planning of research programs are a number of common points of reference--namely, assessment of the state-of-the-art, of the scientific opportunities, and of the national significance of the problem. However, planning at NIH takes many different forms, depending upon the problem and how much is known about it. This variety of planning approaches reflects the great diversity and complexity in the many fields of inquiry that NIH supports and the processes through which knowledge is advanced.

Over the past several years, NIH has strengthened and improved its planning activities in order to ensure that the most promising scientific opportunities are identified and pursued, that limited resources are effectively used, and that NIH programs are responsive to legislative mandates and broad health objectives established by the Department. Highlights of some of the factors considered and processes followed in planning NIH research programs and in establishing priorities are summarized below.

Institute Planning Processes

Each Institute conducts its own planning process through which future program directions are identified, research priorities established, and resource allocations considered. While there are differences, each Institute must consider many similar factors in planning its programs. Differences in planning approaches can be attributed to the nature and scope of the research activity being planned, to the internal resources available, to the individual planning requirements imposed by legislation, organizational behavior, and management style.

In general, each Institute annually--

- Assesses its goals, objectives, and the research strategies designed to meet those goals;
- Reviews program progress, the state-of-the-art, evaluation studies, and various reports addressing particular program areas;
- Assesses scientific opportunities and plans program directions and emphases;
- Attempts to determine the national significance of the health problems under consideration;
- Reviews program contributions to broader health objectives established by PHS and HHS;
- Reviews responsiveness of programs to Congressional mandates; and
- Involves the Institute's National Advisory Council, as well as professional community, in establishing program directions.

These activities all influence the setting of priorities and result in a diverse array of planning documents and program reports. Consideration of these factors provides a basis for recommending program changes to the NIH Director as part of the central NIH planning process.

Central NIH Planning Process

The central NIH planning process provides a structured framework within which overall policies and directions are explored and established, priorities developed, and broad research activities coordinated. It provides a formal means for the Institute Directors and the Director, NIH, to discuss, and make decisions, in balancing scientific opportunities and needs with available resources. This process begins in September/October of each year and has been broadened recently to cover a 12-month period. The major elements in this process are:

- Planning/Appropriation Briefing Sessions. The purpose of these sessions, held in December and January of each year, is to brief the Director, NIH, for the Appropriation Hearings and to provide initial information and justification needed by the Director to establish tentative budget ceilings for the Institutes. These sessions provide a forum for interaction and decision-making between the Director, NIH, the NIH Institute Directors and their respective senior staffs, and result in a mutually useful briefing in preparation for the Congressional hearings, action leading to the resolution of program issues, and initial budget strategies for the planning year.
- Strategy Review Sessions. The purpose of these sessions, held in April this year, between the Director, NIH, and Institute Directors, is to refine the NIH budget strategy for the planning year, establish priorities under varying assumptions and constraints, review the impact of

policy decisions in this context, and establish tentative NIH and Institute budget ceilings. These sessions form the basis of proposals to the Administration and result in a well-defined structure within which the Institutes can plan in greater detail their research programs for the coming year.

- Program Review Sessions. These review sessions, held in the spring/summer months, between the Director, NIH, and Institute Directors, provide an opportunity to explore and consider major program and policy issues of mutual concern, including major NIH policy changes and their implications, issues or problems facing an Institute or Division, long-range program developments and initiatives, reviews of research areas, and planning and evaluation activities. These sessions are not tied to any specific budget event, combine both planning and evaluation concerns without being tied directly to the development of the research or evaluation plan, and provide a forum for the discussion of science as well as management problems.

- Trans-NIH Programs. A number of health problems cut across the categorical lines of the Institutes and require a somewhat different planning effort. These problems are reviewed within the same structure as that provided for the individual Institutes, and each Institute with an interest in the particular health problem participates. Each area reports on the current status of planning in these areas, including assessment of coordinating mechanisms in place and future activities planned, as well as major issues that need to be addressed. If necessary, review sessions are scheduled with the Director, NIH, to discuss these matters.

- Integration of Budget and Research Planning. The budget and research planning processes are integrated at all points throughout the 12-month planning period. This integration provides NIH with a firmer planning base, a more realistic context in which to consider future program directions, and a more relevant structure around which decisions concerning research opportunities can be made. It also advances the NIH capability to develop the agency preliminary budget submission as a logical followthrough of the planning process.

The central planning function also involves the establishment and management of mechanisms designed to address special areas of broad science policy, such as recombinant DNA research, radiation research, and support of toxicological activities. Although concerns and approaches vary greatly depending upon the issues in each area, certain basic planning problems are common to all--namely, how to bring together a variety of interests that cut across different government agencies, institutions, and points of view to focus on common problems, and the development of a process that is both responsive to public pressures and flexible enough to allow for debate and the development of consensus.

Section Two

INSTITUTE AND DIVISION PLANS AND RESEARCH OPPORTUNITIES

Introduction

This section summarizes the plans and opportunities for research progress in the biomedical research and supporting programs conducted and supported by the NIH Institutes and Divisions. These represent highlights of the more comprehensive plans which are developed by the Institutes. Each Institute conducts its own planning process through which future program directions are identified and resource allocations are considered. The Institute planning activities result in a diverse array of program documents which provide more extensive information than the presentations in this section. These separate planning processes feed into the NIH Research Plan cycle and provide the substantive basis for the Planning/Appropriation Briefing Sessions and Strategy Review Sessions. The results of these reviews form the basis of the Institute plans presented here. These plans may be modified in the coming year in order to take advantage of new opportunities as they arise and also to reflect Administration and Congressional changes in the budget.

The sections contained in the Institutes' plans are:

- Director's Preface. This statement provides an indication of the dimensions of the health problems being addressed by each Institute, highlights the research program strategy developed to deal with the problems, and briefly discusses the relevance of this strategy to broader health objectives.

- FY 1981. Examples of areas of research holding great promise for progress and/or major advances and recent accomplishments.

- FY 1982 Program Changes. This portion of the Institutes' plans highlights major activities that are planned to be initiated, maintained, cut back, eliminated, or not started in FY 1982 as a result of the FY 1982 budget process. The intent here is not to address each research program, but to focus on only major program changes.

- FY 1983 Program Changes. This portion highlights major program changes planned for FY 1983, including new initiatives, expansion of ongoing activities, shifts in program emphases, and cut-backs in program.

- Summary of Director's Planning/Appropriation Briefing Sessions. This portion of the plan summarizes some of the highlights and issues discussed at the NIH Director's Planning/Appropriation Briefing Session with each Institute.

The plans which follow are based upon the following budget levels:

Budget--National Institutes of Health, FY 1981 and 1982
(Thousands of Dollars)

Bureau/Institute/Division	1981 Direct Obligations	1982 President's Budget (September)
National Institute on Aging	$ 75,596	$ 74,084
National Institute of Allergy and Infectious Diseases	232,028	214,504
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	369,292	334,923
National Cancer Institute	989,342	902,832
National Institute of Child Health and Human Development	220,366	203,362
National Institute of Dental Research	71,107	65,672
National Institute of Environmental Health Sciences	92,923	96,851
National Eye Institute	117,666	116,445
National Institute of General Medical Sciences	333,504	300,257
National Heart, Lung, and Blood Institute	549,662	510,050
National Institute of Neurological and Communicative Disorders and Stroke	252,182	243,017
Division of Research Resources	175,551	168,839
John E. Fogarty International Center for Advanced Study in the Health Sciences	9,108	8,438
National Library of Medicine	44,660	41,956
Office of the Director	22,465	20,682
Buildings and Facilities	17,054	9,073
TOTAL, NIH	$3,572,506	$3,310,985

NATIONAL INSTITUTE ON AGING

Director's Overview

Since its establishment in 1974, the National Institute on Aging (NIA) has become the focal point within the Federal Government for the promotion of research on aging. NIA has developed and supported research and training programs whose objectives are to promote health and well-being of the aging population so that the vigorous and productive years of life can be extended.

In the past several years, mankind has witnessed a marked increase in longevity and in the numbers of older people. This age group 65 and over is expected to nearly double in size during the next 40 years, moving from about 25 million in 1981 to 45 million by 2020. A significant segment of the over-65 age group now is burdened by age-related disease processes and by the lack of recognition that some age-related disabilities are preventable, reversible, or whose impact can be minimized by compensatory measures. Basic research on aging processes, on age-related diseases and their prevention, and on social factors that impact adversely on the aging population are critical to the endpoint of health cost-containment and the optimization of health and effective functioning for this rapidly growing segment of the population.

The research and training objectives of NIA are developed and supported by the Biomedical Research and Clinical Medicine Program (BRCM), the Social and Behavioral Research Program (SBR), the Epidemiology, Demography, and Biometry Program (EDB), and the intramural research program at the Gerontology Research Center (GRC) in Baltimore. BRCM supports research on basic aging processes, age-related changes of physiological function, and clinical problems. SBR supports research on psychological and social aspects of aging, such as the behavior, attitudes, and status of older people within a changing society. EDB coordinates and conducts quantitative population-based research on health and diseases of the aged. GRC conducts basic research in each of these areas and, with the Baltimore Longitudinal Study Group, composed of men and women, carries out a broad range of clinical studies.

During these formative years, the NIA has utilized a significant portion of its budget for research resource development--i.e., research training, aging animal colonies, and cell banks. These resources were vital to initiate research unique to the field of aging. They were necessary for the transposition of ongoing studies in the fields of behavioral biology, molecular biology, neurobiology, endocrinology, immunology, nutrition, and pharmacology to include the variable of age. They provided early on the opportunity to pose and test hypotheses of basic aging processes and the incipient physiological decline of short-lived but experimentally manageable animal species. This resource, developed and supported by NIA and made available to investigators, allowed generation of new insights of practical clinical as well as fundamental biological significance. Knowledge of reactive synaptogenesis, axoplasmic flow, the dynamics of neurotransmitter function and control, and their relationship to senescence of the central nervous system, and to age-related changes in drug and hormone sensitivity developed with the aged animal colonies and cell banks, provided significant leads that can now be extended to longer-lived species and to humans. Because of this early emphasis, NIA has developed testable hypotheses of the mechanisms of aging, clinical and psychosocial correlates of aging, as well as potential behavioral, pharmacological, immunological, and nutritional approaches by which the onset and severity of age-related phenomena can be influenced.

An assessment of the current status of aging research provides impetus for a shift to studies with longer-lived animals and with human subjects. Future initiatives of NIA will emphasize research and manpower development for clinical studies, the development of human population studies, and the establishment of colonies of aged long-lived animals such as cats, dogs, and nonhuman primates. These initiatives should enable NIA to implement its clinical research program with special emphasis on disease prevention and health promotion.

Program and Research Accomplishments During Fiscal Year 1981

Program Reorganization

During FY 1981 the National Institute on Aging (NIA) received authorization for reorganization of the BRCM, SBR, and EDB programs. BRCM is now composed of the Geriatrics Branch, Physiology of Aging Branch, and Molecular and Cellular Biology Branch. SBR is composed of the sections Older People in a Changing Society, Cognitive and Biopsychological Aging, and Older People and Social Institutions. EDB is composed of the sections Epidemiology, Demography and Economics, and Biometry.

The National Research Plan on Aging

NIA is developing the National Research Plan on Aging. A scientific panel developed the Aging Research Program structure consisting of a specific goal, four subgoals, a set of issues for each, and a set of subissues for each issue.

The panel has commissioned 250 scientific papers, each addressing a subissue. These will be analyzed by task groups with reports prepared for submission to the subpanels. Each report will be analyzed and integrated for the four subpanel reports. From the latter, the National Plan will be prepared by the full panel. The latter is scheduled for release by March 1982.

Research Accomplishments, FY 1981

Senile Dementia of the Alzheimer's Type (SDAT). Studies on the etiology of SDAT indicate:

- A marked decrease in brain hippocampal choline acetyltransferase activity occurs in patients with this disease. Thus, procedures that might elevate acetylcholine formation--i.e., increased dietary lecithin--or inhibit acetylcholine breakdown--i.e., administration of cholinesterase inhibitors, such as physostigmine or nysostigmine, are potential therapeutic measures to be evaluated.

- An elevated hippocampal aluminum content has been observed in individuals with this disease, and similar brain lesions have been produced in rodents by injection of aluminum salts. Studies with chelating or coordinating agents that interact with and promote excretion of aluminum ions are being developed.

- Brain neurons of rodents can produce new axons and form new synapses. Regrowth is much less extensive in aged than in younger animals and seems to be suppressed by glucocorticoids. If endocrine imbalance influences plasticity, then it may be possible to rejuvinate synaptic growth in aged brain.

Functioning and Productivity in Later Life. Investigation to identify conditions to maintain and improve ability to function and be productive indicate:

- Cognition and memory depend less on age than on education and environment. Intellectual decline with aging can be slowed by simple training interventions.

- The effects of some visual impairments can be partially offset by the use of typefaces of particular styles (Roman) and size (twelve point).

- Age-related changes in olfactory and gustatory senses which alter eating habits and lead to malnutrition can be compensated by specific dietary additives. Certain amino acid derivatives such as glycinamide are discerned as salty, and therefore could be substituted for salt in the diet.

Geriatrics. Research in geriatrics has demonstrated:

- That minimal mortality in the over-65 age group occurs in the 10 to 20 percent over-desirable-weight range, as currently defined by life insurance tables (Baltimore Longitudinal Study Group). This relationship has been confirmed from the published data of 45 other population studies of obesity versus mortality.

- That progressive glucose intolerance is correlated with aging and with mortality, but not with the clinical manifestations of diabetes mellitus. This recognition should reduce the need for and costs of clinical services for about 20 percent, or approximately 6 million people, in the 60-to-80 age group.

- That benign prostatic hyperplasia in dogs, and probably in man, is characterized by an estrogen-augmented accumulation by the prostate of dihydrotestosterone and its receptor protein. The possibility exists that blocking the synthesis or action of the estrogen would inhibit growth or induce regression without causing impotence.

Biology of Aging

- T-cell immunologic functions decline with age but can be maintained in rodents by dietary restriction.

- The senescent rat manifests impaired motor functions comparable to those seen in younger rats subjected to damage to specific dopaminergic neurons. The age-related impairment can be partially reversed by dopamine-agonist drugs.

- A generalized review of basic mechanisms of aging, developed for the NIA Conference on Biological Mechanisms of Aging, emphasized that the "error theory of aging"--that errors in transcription or translation during protein synthesis may accumulate during aging--does not appear to explain the changes in structure and function that characterize specific proteins of aged individuals. Other theories of aging will be subjected to the same rigid scrutiny.

FY 1982 Priorities and Major Program Changes

Given the 1982 planning assumption coupled with requirements to stabilize research project grants, NIA will emphasize the following priority areas. This will require reduction in support of manpower development.

Senile Dementia of the Alzheimer's Type (SDAT)

A major program on researchable issues related to SDAT will be continued. Planned studies include:

- Epidemiology. These studies will focus on the prevalence and natural history of SDAT. Research will focus on noninstitutionalized persons and seek to identify the medical and behavioral antecedents characterizing those subjects that develop SDAT.

- Etiology. NIA will support investigations designed to evaluate the relationship of SDAT to neurotransmitter and endocrine imbalances, immunological deficiency, slow viruses, and environmental factors such as aluminum and other possible etiological agents.

- Diagnosis. Research emphasis will be given to the design, development, and improvement of methods for the diagnosis of SDAT. Basic, clinical, and epidemiological research will be supported that defines the anatomical changes and clinical expressions of SDAT, as well as the psychological and social consequences.

- Pharmacology. Research on therapeutic intervention in SDAT will focus on neuropharmacological agents that increase brain levels of cholinergic neurotransmitters. In addition, studies will be encouraged to develop pharmacological agents that minimize memory and cognitive losses.

- Incontinence, Falls, and Sleep Disturbances. Research will be initiated to evaluate occurrences of these conditions in relation to that of SDAT, since they have a common relationship to impaired functions of the central nervous system (CNS).

Geriatrics

NIA will encourage the development and support of basic and clinical studies related to the clinical, psychological, and social aspects of aging and basic aging processes.

- Physiology of Aging. Research projects designed to delineate the cellular and molecular basis of aging processes in laboratory animals and their extrapolation to humans will be encouraged. These studies will seek to determine the effects of endocrine and nutritional factors on aging and the pathophysiological correlates of aging such as diabetes, vascular diseases, cancer, increased prevalence of infection, and immunosenescence.

- Longitudinal Studies. The further development of longitudinal studies will be encouraged. Intramural research will be continued to study a variety of medical conditions and behavioral changes associated with age in men and women. Extramural research will be developed around preestablished community-based populations. Epidemiological studies on health and diseases of the aged, as well as social and psychological factors, will be explored.

- Pharmacology. Studies will be developed to identify drug usage in the elderly, drug-drug interactions, and the risks of adverse drug reactions, particularly in the treatment of chronic conditions common to the aged. NIA will also encourage expanded studies of age-related changes of intestinal absorption that could decrease drug response, and decreased microsomal enzyme activity that could increase drug response and consequent adverse drug reactions.

- Immunology. Basic and clinical studies of immunological function will be continued, emphasizing studies characterizing changes in specific antibody production, granulocyte, and T-cell function, as well as techniques to modify or reverse age-related immunological changes.

- Nutrition. NIA will continue to emphasize the relationship of nutrition to the health of the aged, with particular attention to the development of clinical and population-based studies. This research will include studies of effects of diet, weight, and physical exercise in modifying immune, endocrine, and metabolic processes with age, as well as the effects of psychological, social, and economic factors which affect dietary patterns of the aging individual.

- Senile Osteoporosis. Since osteoporosis is a major public health problem, particularly in postmenopausal women, studies will be continued on the pathogenesis of osteoporosis and the clinical expression of age-related bone loss in both men and women. Basic to this project is a more complete understanding of bone cell metabolism during senescence, its control by endocrine factors, exercise, and the development of more simple diagnostic techniques.

Functioning and Productivity

This major program of research encourages studies of the social and behavioral factors that, interacting with biological factors, can extend the productive middle years of life, prevent and postpone old-age disability, and contain costs to individuals and society of health care and dependency. Studies will focus on:

- Family and Household. Intergenerational exchanges of material and emotional support. Maintenance of older people in their own homes. Health consequences of bereavement. Coping with reduced income and social isolation.

- Work and Retirement. Physical and psychological capacities and motivations for continuing productivity and creativity. Aspects of work situations that stimulate intellectual competence, provide incentives and opportunities for retraining and occupational shifts. Retirement as beneficial versus health-threatening and status-reducing.

- Health and Health Institutions. Life style changes that can maintain health, prevent disease. Social changes (e.g., economic fluctuations, urbanization) and psychosocial stresses as contributors to pathogenesis. Social supports, coping, health attitudes and behaviors as sources of renewed functioning and independence, even among disabled older people.

- Methodology. Improved measures to evaluate human performance. Improved longitudinal and cohort designs to evaluate interrelationships between psychosocial and biomedical aging and estimate future changes in the older population.

FY 1983 Major Program Changes

Greater understanding of the mechanisms underlying time-dependent and age-related changes is necessary to enhance the quality of life for older people and to contain the costs of health care and dependency. A considered appraisal of the current stage of development of aging research indicates that

NIA needs to increase its base of investigator-initiated research, specialized clinical investigation capabilities, research resources and manpower, and intramural clinical research programs.

Therefore, NIA plans to support:

- An increase of research project grants from 382 in FY 1982 to 404. This increase will maintain a 15 percent increase in the FY 1983 commitment base of research grants and decrease slightly (6.5 percent) the award level of competing research grant applications. Support for the SDAT initiative and geriatrics, pharmacology, nutrition, and social and behavioral research would be slightly increased.
- The development and implementation of five teaching/nursing home research centers that provide training and environment for clinical investigation in medical and psychosocial research issues of importance in all of the aged.
- An increase of 16 awards for the development of research manpower to support clinical research on aging (academic awards). From 42 in FY 1982 to 54 in FY 1983.
- An increase in individual and institutional research training awards to ensure the future availability of well-trained investigators at a level commensurate with the planned expansion of the Institute's support of research grants.
- Implementation of the development of long-lived animals and data base resources.
- Increase number of staff of the Baltimore Longitudinal Study by 28 to support increase of females in study group.
- Increase size and scope of the NIA Intramural Neurosciences Program to support expanded clinical studies.

Potential Impact of Program Changes, FY 1983-85

The program changes proposed in FY 1983 will impact heavily on NIA's biomedical, social, and behavioral research programs over the next three fiscal years.

In view of NIA's plans in FY 1983 to initiate a program of clinical investigation emphasizing the teaching/nursing home, a broader based research manpower development program must be initiated. This program will be necessary to provide trained clinical investigators in geriatrics that will form the core of the research programs on teaching/nursing home. Therefore, over the next several years, increased support will be necessary for academic awards in geriatrics.

Concurrent with the increased emphasis on clinical investigation and increase in the research grants support is a requirement to increase support of animal, cellular, and other research resources in quality, quantity, and definition. The research resource needs for NIA will be entering a new phase in FY 1983. Resource development must be continued to support characterized and defined short-lived animals and cellular resources. Primary emphasis must be shifted to more specialized resources of longer-lived animals, differentiated cells, tissues, organ, and fluid banks, human populations, data based banks. This will necessitate modest resource program changes in FY 1983 that must be accelerated in subsequent years to keep pace with an intensified research program in SDAT, nutrition, pharmacology, and social and behavioral research.

Enhancement of the neuroscience program will at the outset require only modest fiscal and personnel support. Future years' development of this program will require the commitment of technical and logistic support in terms of equipment, space, and personnel, particularly if the full implications for clinical investigation into SDAT are to be fully realized.

NIA plans to shift research attention to studies on human health and effective functioning in the later years. In the early stages, the development of this program will require identification and categorization of ongoing research activities to assemble a critical mass of studies. Subsequent years will require increased research support for development of an effective research plan for this important area.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Institute on Aging

DATE: FEB 10 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I was pleased to learn that a major effort of the Institute during FY 1981 is to develop a National Research Plan on Aging. This effort should help considerably in formulating a long-term strategy for promoting the health and well-being of the aged population. I would encourage you to address not only areas of emphasis and opportunity in your plan, but also a strategy for relating opportunities to resources available during periods of economic constraint. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

D S Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

The research of the National Institute on Aging (NIA) takes on heightened significance because of the consistent increase in the aged population of the United States, and because health care costs are higher for the elderly. The number of elderly people in nursing homes accounts for a disproportionately large share of all the health care expenditures for their age group. Research to develop methods for the treatment and prevention of senile dementia of the Alzheimer's type, decubitus ulcers, and incontinence could lead to significant reductions in the health care costs for the Nation.

Impact of Stabilization

- The total number of research project grants will remain relatively stable during the years 1981-83. However, the number of competing awards will drop substantially in 1983 if additional funds are not made available.

- The number of individual and institutional training awards will decline in 1982, representing a reduction in the number of trainees (FTEs)* supported.

- Contracts will be held essentially constant. The contract mechanism is used, in part, to fund research resources--such as colonies of aged research animals--which are necessary for much grant-funded research. Reductions in contract funds would place in jeopardy the continuing availability of needed resources and would serve only to transfer the expenses to individual grants, thereby indirectly reducing the funds available to investigators.

- The Intramural Research Program will remain at about the same level of activity during the 1981-83 period.

- The stabilization initiative has adversely affected the NIA's capacity to emphasize clinical investigations and psychosocial research, and has slowed the development of research resources, such as aging animal colonies and cell banks, and trained manpower.

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* Full-time equivalents.

Recent Research Activities

- Progressive glucose intolerance in human subjects that is not necessarily associated with other clinical manifestations of diabetes mellitus has been correlated with aging. Recognition of this relationship could reduce the need for clinical services for many older people who are now diagnosed as diabetic on the basis of glucose tolerance tests.

- Specific training interventions have been found effective in slowing the intellectual decline associated with aging.

- Specific efforts have been organized to disseminate to physicians information that will allow differentiation of reversible forms of dementia from Senile Dementia of the Alzheimer's Type (SDAT).

- Marked decrease of brain choline acetylase activity has been noted in patients with SDAT. Procedures that could elevate brain acetycholine synthesis, such as elevated dietary lecithin, or decrease acetycholine breakdown, such as cholinesterase inhibitors, will be evaluated.

- Benign prostatic hyperplasia in dogs and man is characterized by an estrogen-augmented accumulation by the prostate of dihydrotestosterone, a specific cell growth factor, and its receptor protein. Thus, blocking the synthesis or action of the estrogen could inhibit growth or induce regression without causing impotence.

- New techniques are being studied which may reduce the incidence and severity of incontinence, a major factor determining nursing home placement.

Special Program Activities

- P.L. 96-171 (Experienced Pilots Study) directs NIH to conduct a study to determine if an age limitation for commercial airline pilots is medically warranted. In June 1980, NIA contracted with the Institute of Medicine (IOM) of the National Academy of Sciences to examine, summarize, and assess the existing medical and scientific data relevant to the study objectives. The IOM report will provide the data base for the development of the NIA report scheduled for transmittal to Congress on September 30, 1981.

- The White House Conference on Aging is scheduled for November 29, through December 4, 1981, and will develop recommendations for further research and action in the field of aging. NIA has taken an active role in planning the conference and has commissioned scientific papers of high interest. The Institute is providing funds for selected mini-conferences where research is a prominent agenda item, will prepare special exhibits for the conference, and may present a preliminary National Research Plan on Aging to the White House Conference.

- A Plan of Work has been developed which would serve as the basis for NIA to be designated as a World Health Organization (WHO) Collaborating Center for Joint Cooperation on Research on the Care of the Aged.

Action Item

The concept under which the Geriatric Research Centers (Teaching Research Nursing Homes) would be established is sound; however, much planning remains which is critical to implementing this concept.

Research Manpower Development

Statement of Issue

Emphasis on the ongoing support of manpower development in both preclinical and clinical geriatric research is a fundamental strategy of NIA.

While NIA has implemented several academic award mechanisms, the deemphasis of research manpower development since the establishment of NIA has resulted in undercapitalization during a period of significant growth of the research base. In particular, the shortage of scientists qualified to conduct clinical investigations will compromise the thrust that NIA hopes to implement in the future.

Discussion of Issue

A review of manpower development and research programs supported by NIA revealed approximately 165 trainees and 400 research grants in both 1980 and 1981. With appropriate adjustment for the mix of P01 and R01, this translates into a principal investigator-to-trainee ratio (FTE) of approximately 2.8. This reflects a manpower development program insufficient to compensate for the established attrition rate for long-term maintenance of the research base of NIA. Furthermore, the distribution of pre- and post-Ph.D. and M.D. trainees within the existing trainee pool reveals a critical need for additional clinical scientist trainees. It is clear that stabilization of the training base at current levels would not support the future clinical research emphasis planned by NIA.

Alternatives and/or Suggested Position

By our assessment, two issues are critical to assuring the future manpower needs of research supported by NIA. The first addressed the specific kinds of scientists required and the second addresses the policies necessary for resolution of the problem. Biomedical and social/behavioral research programs require principal investigators with multidisciplinary training backgrounds. Furthermore, those qualified to conduct clinical investigation in geriatric medicine should be identified early in the medical curriculum and stimulated to choose electives that emphasize geriatric medicine and clinical research during their predoctoral training period.

These measures will require a broad and flexible NIH policy that recognizes and is designed to meet specific needs of each BID.

Research Resources

Statement of Issue

The research resource needs for NIA will enter a new phase early in FY 1982. Support for development, characterization, and monitoring of the availability of short-lived animals and cellular and biological materials will be maintained or slightly increased. Emphasis on resource development must be shifted to more specialized resources of long-lived animals, tissue organ and fluid banks, human populations, data base analysis, and data base banks.

Discussion of Issue

NIA is committed to the maintenance of current programs of basic research on the mechanisms of aging, on the clinical and psychosocial correlates of aging, and on pharmacological, nutritional, immunological, psychological and educational approaches to delay the onset or minimize the severity of those conditions. However, in order to hasten the extrapolation of those research findings and extend their application to aging human subjects, long-term commitment to the support of additional resource development will be required. These resources are essential to the maintenance of the current and future research base of NIA.

The specific projects proposed include:

- The development of colonies of longer-lived rodents for studies on aging;
- The use and further development of existing dog, cat, and nonhuman primate colonies for studies on aging;
- The development of techniques for and maintenance of differentiated mammalian cells;
- The development of banks of aged human and animal tissues, cells, and fluids;
- The development or expansion of social, economic, and medical data base resources, so that secondary analysis of research issues can be accomplished efficiently on existing data sets; and
- The development of specialized human populations for clinical and sociological studies on aging.

Alternatives and/or Suggested Position

NIA has few if any alternatives to the development of critical resources needed to support aging research. The natural progression of the research program of NIA from basic to emphasis on clinical investigation requires aged animals, resources, human populations, and data base banks. In view of the long lead time necessary for development of resources for aging research and their unique characteristics, NIA must frequently assume sole support of the resource development. It is NIA's position that resource development will be shared wherever possible. This approach has already been implemented with the development of an aged primate resource with DRR. For these reasons, support of resources should be separated from the science base; otherwise, NIA research programs may be delayed inordinately.

Experienced Pilots Study

Statement of the Anticipated Appropriation Hearings Issue

P.L. 96-171 directs NIH to conduct a study to determine whether a mandatory age limitation of 60, or any age limitation, for commercial airline pilots is medically warranted. The NIA, designated by NIH as the lead Institute in this effort, established in January 1980 an Inter-Institute Committee, with representation from NIA, NHLBI, NINCDS, and NIMH, to oversee study implementation and the preparation of the final report to Congress. In June 1980, NIA contracted with the Institute of Medicine (IOM) of the National Academy of Sciences to examine, summarize, and assess the existing medical and scientific data relevant to the study objectives. Following submission of the IOM report to the NIA in late March 1981, the NIA will make the IOM report available for public comment, conduct a series of meetings on the subject, and prepare a final report to Congress based on these meetings and the IOM report. It is anticipated that the final report will be transmitted to Congress on September 30, 1981.

Discussion of Issue

The Experimental Pilots Study is a highly visible activity with great Congressional, press, and public interest. Statements before Congressional committees, statements of Members of Congress, Congressional correspondence to the NIH and NIA, and news articles reflect varied points of view regarding the issue of an upper age limitation for commercial airline pilots. For example, the Federal Aviation Administration testified against the enactment of legislation which would amend the so-called "age 60 rule" by statute. A numer of organizations, such as the Pilots' Rights Association, have testified in favor of eliminating the present age 60 limitation by legislation.

The IOM report is now in its last draft. After it is issued in early spring, it will become widely available for public comment. An NIH panel will meet three times during the spring and summer of 1981 to review the report for completeness and accuracy, analyze public comments, and prepare the NIH report. It is expected that the NIH report will be finished in July and, after Departmental review, be released to Congress by September 30, 1981.

Status Report on HHS Health Research Initiative

Senile Dementia of the Alzheimer's Type

The description of this initiative contained in the December 1980 HHS Health Research Planning document remains accurate. The budget estimates collected by the Division of Financial Management have been confirmed with other participating BIDs, and no changes in future plans have been identified.

As the lead Institute for this initiative, NIA has placed special emphasis on assembling a base of investigations and exploiting research opportunities on Senile Dementias of the Alzheimer's type (SDAT). As reflected in the Institute's FY 1982 and 1983 plans, research on SDAT is a major priority and an area around which Institute programs coalesce. Simultaneously, NIA is laying the groundwork for more closely defined relationships and enhanced collaboration among cosponsors of the initiative through:

- a joint program announcement with NINCDS (under development);
- cosponsorship with NINCDS and NIMH of a mini-conference on Alzheimer's Disease and Related Disorders, convened by the Alzheimer's Disease and Related Disorders Association under the auspices of the White House Conference on Aging; and
- plans to convene a small NIA working group which will meet periodically to review and assess advances in neurochemistry relevant to SDAT and to evaluate various treatment modalities designed to ameliorate symptoms in the Alzheimer patient. Representatives from other BIDs and HHS agencies will be invited to participate as appropriate.

National Research Plan on Aging

A major effort of the NIA during FY 1981 is the development of a National Research Plan on Aging, with the assistance of a panel of 22 scientists. This panel will advise the NIA in its formulation of a five-year strategy for promoting the health and well-being of the aged population through research into the biomedical, behavioral, and social aspects of aging. The broad objectives of the Plan are to:

- Provide a stable, long-term framework for conducting research on aging;
- Establish a sound, scientific basis for setting priorities;
- Identify areas where interdisciplinary and multidisciplinary approaches offer the most promise;
- Communicate to the President, Congress, scientific community, and the public progress to date and future needs in aging research;
- Provide an organized, comprehensive view of aging research for use during the activities associated with the 1981 White House Conference on Aging;
- Identify opportunities in aging research which will attract scientists to the field.

As a basis for developing the National Plan, the panel will be provided with the results of an inventory of Federally supported aging research and training activities. A related evaluation of the NIA Animal Resources and Genetic and Cellular Resources Program will assist the Panel in identifying those resources needed to implement the plan.

NIA International Activities

World Health Organization and the United Nations World Assembly on the Elderly

In May 1979 the World Health Organization (WHO) adopted a Resolution on Health Care of the Elderly which called for collaboration with the 1982 United Nations World Assembly on the Elderly. The following events associated with this Resolution and NIA have either occurred or are being planned:

- Establishment in 1980 of the WHO Global Programme on the Care of the Aged, located in Denmark and managed by Dr. David McFadyen.
- A major presentation at the May 1980 meeting of the National Advisory Council on Aging on international developments in aging, with a panel of speakers and guests.
- Drafting of a Plan of Work which would serve as the basis for the Institute to be designated as a WHO Collaborating Center for Joint Cooperation on Research on the Care of the Aged. The agreement has been conceptually cleared. The Secretary General is expected to seek endorsement of the PHS Surgeon General before the end of June 1980.
- WHO preparatory Conference for the U.N. World Assembly on the Elderly, Mexico City, December 1980, for which NIA provided grant support of $90,000.
- Hosting of about 18 WHO-sponsored Directors of National Institutes of Gerontology during the November/December 1981 U.S. White House Conference on Aging, during which they will observe and participate in the Conference. They will also hold an Executive Session following the Conference to further address their contribution to the UNWAE.
- Finally, Organization of the United Nations World Assembly on the Elderly (UNWAE). Mr. John MacDonald, Deputy Assistant Secretary of State for International Organization Affairs, has been named the WAE U.S. Coordinator for the Assembly which is expected to be held in San Francisco the last week of August and first week of September 1982. NIA has been involved in the early development of this Assembly and has promoted the importance of cross-national and comparative research as an integral part of the developmental and humanitarian issues to be addressed. A meeting was held between the NIA Director and the U.S. Coordinator at which time NIA was requested to provide such support as assignment of personnel to serve as and staff an Office of the WAE Secretariat at the Department of State.

Model Teaching/Research Nursing Homes

The NIA is exploring the feasibility of establishing model teaching-research nursing homes at academic medical institutions. Such nursing homes would be patterned after teaching hospitals, which historically have played a key role in advancing clinical medicine, medical education, and research, especially for acute care. The teaching/research nursing home could serve a similar function to address critical development needs for geriatric medicine and provide an environment to pursue the following goals:

- Foster systematic clinical investigations of disease processes in the aged, and develop diagnostic techniques (especially comprehensive assessment procedures) and methods of treatment adapted specifically for the elderly;

- Train geriatricians, physicians in traditional specialities heavily utilized by the elderly, geriatric and other nurses, and a variety of other urgently needed professionals (in the education of physicians and allied medical personnel, there is a lack of exposure to nursing home patients and their special problems, even though they consume a vast amount of health resources);

- Lay a research base for (a) improving care in nursing homes and in physician practices, (b) designing community services and clinical strategies for postponing or preventing institutionalization, and (c) rehabilitating and rapidly returning patients to their own homes; and

- Devise and demonstrate cost-containment strategies.

The teaching/research nursing home was one of the major issues raised in the Research Task Force on Long Term Care organized by the Under Secretary, HHS. The rationale underlying this proposal and the possibility of convening a task force of experts to develop an implementation plan have been presented to the Secretary, HHS. An informal opinion was obtained from General Counsel in December indicating that NIA has legal authority to assume lead responsibility for coordinating such a task force, and formulating an implementation plan. The opinion included a caveat concerning NIA implementation of certain types of activities that might be called for in such a plan. While NIA plans to actively pursue the further development of this proposal, the Institute is acutely sensitive to the need to collaborate with other affected agencies and HHS components and to frame the initiative in a manner consistent with the Institute's mission.

PROGRAM PERFORMANCE SUMMARY

GERIATRIC RESEARCH

Program Description

Scope of Work

The National Institute on Aging (NIA) is mandated by Congress to conduct and support biomedical, social, and behavioral research and research manpower development that relate to the aging process and the diseases and other special problems and needs of the elderly. In the past 80 years, the segment of the U.S. population over 60 years of age has increased from 4 percent of the population to 11 percent and is expected to rise to between 17 and 23 percent during the next 40 years. These changes represent the combined benefits of social, economic, and medical progress. On the other hand, the incidence of illness and disability is strongly correlated with advancing age. Therefore, it is certain that, as the number of aged individuals increases, the magnitude of health care problems and the costs, which are to a large extent financed by public funds, will also increase unless geriatric health care becomes more efficient. Furthermore, more appropriate and effective health care during the middle and later years of life should enhance the quality of life as well as productivity and independence during the later years.

To implement its mandate, and to improve the quality and efficiency of geriatric health care, NIA supports research to develop a detailed understanding of the processes of normal aging and the mechanisms by which they render the individual more vulnerable to disability and disease. Geriatric research is defined as encompassing all investigations that involve clinical studies of human subjects which attempt to clarify the mechanisms by which aging causes an individual to be more susceptible to disease and disability or which attempt to prevent or reverse these mechanisms. Currently, geriatric research encompasses research to describe risk factors, etiology, and appropriate therapy for senile dementia of the Alzheimer's type, depression, osteoporosis, benign prostatic hypertrophy, incontinence, immunosenescence, as well as characterization of the role and efficacy of social support, coping, and psychosocial interventions in prevention or alleviation of the physiological decline that accompanies aging.

The NIA has three programs that develop and direct extramural research of the Institute with respect to specific scientific disciplines: the Biomedical Research and Clinical Medicine Program; the Social and Behavioral Research Program; and the Epidemiology, Demography, and Biometry Program. The Geriatric Research Program of NIA is multidisciplinary in that its implementation has been developed by each of these administrative programs. The Epidemiology, Demography, and Biometry Program (EDBP) is developing mechanisms to identify and assess risk factors, etiology, and the clinical course associated with age-related diseases, such as those described previously. The Social and Behavioral Research Program (SBRP) is developing approaches to encourage and support research to describe and evaluate the roles of psychosocial and behavioral factors that influence age-related morbidity. The Biomedical Research and Clinical Medicine Program (BRCMP) supports research on the molecular, cellular, and physiological bases of disease processes associated with aging and their diagnosis, prevention, and treatment.

Information developed by or derived from research supported by these three programs is integrated, and position papers on geriatric research are prepared for use in the NIA planning processes and are distributed through the NIA Annual Report.

Legislative History

The Research on Aging Act of 1974 (P.L. 93-296) amended the Public Health Service Act by establishing the National Institute on Aging.

> "Section 461. The Secretary shall establish in the Service an institute to be known as the National Institute on Aging for the conduct and support of biomedical, social, and behavioral research and training related to the aging process and the diseases and other special problems and needs of the aged."

Section 464 directs the Secretary, Institute, and the National Advisory Council on Aging to develop a plan for a research program that coordinates and promotes research into the biological, medical, psychological, social, educational, and economic aspects of aging.

Objectives and Activities of the Geriatric Research Program

Objectives

The NIA Geriatric Research Program is multidisciplinary. It seeks to encourage the acquisition of laboratory, clinical, and epidemiological data derived from biomedical and behavioral studies of health and disease processes associated with the physiological decline of aging.

Program objectives include:

- Increase the pertinent epidemiologic data on prevalence, incidence, risk factors, complications, and efficacy of therapy for the major sources of morbidity among the elderly, particulary on dementia, incontinence, hypo- and hyperthermia, pneumonia, osteoporosis, osteoarthritis, fall injuries, and decubitus ulcers.

- Determine normal age-related changes of those physiological functions related to the development of major causes of morbidity and mortality in the elderly. (Determination of normal values for these functions in the elderly is essential for the evaluation of etiologic or predisposing factors for disorders of old age. Factors regulating cognition, memory, temperature regulation, sleep, medications, resistance to infection, and bone metabolism are of particular importance.)

- Improve understanding of the etiology and pathophysiology of the above disorders.
- Elucidate the differences between "normal" age-related changes and those that contribute to these disorders.
- Evaluate effectiveness of current and new techniques for the diagnosis, prevention, treatment, or cure of these disorders.
- Determine, specify, describe, and evaluate the psychosocial, biopsychological, and behavioral factors, mechanisms, antecedents, and consequences associated in the elderly with health and effective functioning in terms of positive lifestyle, social support, and coping with stress; and with morbidity and disability in terms of description and diagnosis, etiology, natural course, prevention, treatment, and consequences.

Current Program Activity

Ongoing research is studying a number of disorders concentrated among older people. These include dementia, osteoporosis, benign prostatic hypertrophy, and urinary incontinence. Other circumstances associated with increased morbidity or mortality include fall injuries and infectious diseases such as pneumonia. The medical management of these problems is complicated by underlying physiological changes with age and by frequent presence of multiple disorders often necessitating altered therapeutic strategies.

Geriatric research only recently became a major focus of the behavioral science program of NIA. Nevertheless, nearly one-third of the total research grants managed by the program support research on the role of psychosocial and biopsychological factors and mechanisms in the etiology, natural course, prevention, treatment, and consequences of disease and disability in the aging. Results of the research established that the socioenvironmental matrix to which the older person is exposed is related to health maintenance and the onset and course of disease and disability. Major physiological systems (neurochemical, immune, and endocrine) were shown to be vulnerable to psychological and socioenvironmental factors.

A prospective epidemiological study has shown that the middle-aged person who followed certain behavioral practices would live 7 to 11 years longer than those who followed few or none of those practices. There is additional evidence that social support, coping, and some psychosocial interventions can prevent or alleviate some illnesses, enhance the healing process, and reduce the utilization of expensive medical services.(1)

Evidence of Program Performance

Types of Information Available

- Grant funding data;
- Grant progress reports;
- Published papers, conference or workshop proceedings;
- Position papers prepared by program staff; and
- State-of-the-science assessments and recommendations by consultants to NIA.

Evidence for Assessment of Program Efficiency*

The data presented in Table 1 below indicate the level of support by all segments since initiation of the Geriatric Research Program. During that period, a substantial body of knowledge was acquired. An epidemiological study of international differences in mortality rates is adding to knowledge of genetic and environmental risk for major factors diseases. Epidemiologic studies have examined the role of physical activity and endocrine and dietary factors in the development and prevention of osteoporosis, and have elucidated further details of the relationship of osteoporosis to other risk factors for fractures.(2)

Clinical studies on response to exposure to cold have shown an impairment in vasoconstriction with age that may contribute to the increased incidence of hypothermia in the elderly. Studies using an animal model of osteoarthritis have increased knowledge of cartilage changes with age that predispose to this condition.(3) Clinical studies to elucidate neural and vascular problems associated with impotence in elderly men are in progress. Studies on defects in extraneural tissue associated with Alzheimer's disease should clarify the pathophysiology of this disorder and facilitate antemortem studies.

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*Unreferenced research findings were obtained from research grant progress reports.

Table 1: Funding of the Program in Geriatric Research, FY 1978-81

(Dollars in Thousands;
Number of Awards in Parentheses)

	1978		1979		1980		1981	
Grants								
R01	$1,810	(24)	$4,494	(71)	$5,015	(67)	$6,263	(76)
P01	1,471	(5)	3,103	(12)	5,010	(16)	5,182	(14)
Centers	-		-		-		-	
Other	462	(7)	749	(16)	1,068	(23)	832	(17)
Contracts	-		259	(3)	-		1,224	(4)
Training								
NRSA	90	(3)	95	(3)	100	(3)	100	(3)
	$3,833		$8,700		$11,193		$13,601	
Percent of NIA Budget	10%		15%		16%		18%	

NIA-supported studies on dementia have elucidated more clearly the relationship between cerebral cholinergic deficits and loss of cognitive function, between cholinergic deficits and possible somatostatin deficits, and between intraneuronal aluminum accumulation and neuronal pathology. The NIA has supported preliminary trials of cholinergic and other agents in the treatment of dementia, and has supported the development of a battery of cognitive tests to evaluate the results of these agents.(4)

Benign prostatic hypertrophy (BPH) is manifested after the age of 50 and, by 70 to 80, is apparent to some extent in 75 percent of individuals examined.

Research supported by NIA has established that BPH is associated with an intracellular accumulation by the prostate of dihydrotestosterone and increased levels of its receptor protein.(5) These events associated with hyperplasia are augmented by elevated blood estrogen levels. The possibility exists that blocking the synthesis or action of estrogen would inhibit growth or induce regression of the enlarged prostate without causing impotence.

A large project has been initiated to obtain a wide range of clinical pathologic data from autopsy and surgical specimens. These studies will be valuable in establishing data on normal and pathologic changes with age in man. Another project to study changes with age of mechanical and ultrasonic properties of human bone was recently begun and should yield important data in regard to osteoporosis and risk of fracture.

Research in behavioral science supported by NIA has revealed:

- People in different cohorts exposed to different sociological and psychological conditions do not age in the same ways. Thus, longitudinal cohort studies provide a more realistic assessment of the effects of aging than do cross-sectional studies.
- The aging process and associated physiological decline is not irreversible. Age-related decline in memory and cognition can be slowed by training strategies. The age-related increase in taste threshold for salt and resultant risk of hypertension can be compensated by dietary substitutes that decrease salt intake.
- The relative effects of stress tend to increase with age. Furthermore, mortality associated with bereavement for widowers is greater than for widows.

Manpower development for geriatric research has been initiated through program announcements for the Clinical Investigator Award, the Geriatric Medicine Academic Award, the Geriatric Dentistry Academic Award, the New Investigator Award, and the Research Career Development Award.

Studies Now Under Way

A National Plan for Aging Research is being developed by a group of nationally recognized scientists representing each of the disciplines indicated in the Congressional mandate for NIA. The elements of Geriatric Research constitute one of four focal areas of the National Plan for Aging Research. In addition, a National Inventory of Aging Research is being prepared that will catalog research on aging supported by selected Federal agencies. These will be used by the extramural programs of NIA to help evaluate ongoing research and develop high-priority research programs for the future.

With HHS evaluation set-aside funds, NIA will carry out an evaluation of the Geriatric Medicine Academic Award program. The two general purposes of the evaluation are (1) to assess the overall impact of the program, and (2) to identify, from the several projects and grantee institutions, the characteristics and approaches in terms of indicators of success.

Proposed Studies

The Epidemiology, Demography, and Biometry Program and the Social and Behavioral Research Program have requested authorization to implement specific advisory committees to review and evaluate sponsored research and to recommend appropriate future research emphases.

Major Issues or Problems of Programs Cited by Governmental Organizations or Interest Groups

The 1971 White House Conference on Aging recommended establishment of a National Institute on Gerontology to support and conduct research and training in the biomedical and social-behavioral aspects of aging.(6)

Following authorization by Congress in 1974, the National Institute on Aging initiated development of a research and training plan. The National Advisory Council on Aging reviewed the body of scientific knowledge on aging and recommended specific research approaches to address the needs of the elderly.(7)

The manpower needs for geriatric medicine and research recognized in publications from NIA(8) have been recently updated.(9) Recommendations include increased numbers of physicians and health care specialists with experience with elderly persons as well as social and biomedical scientists trained in the several disciplines required for research in gerontology.

The medical and financial impact of clinical geriatric problems has been frequently cited by the Executive Branch, Congressional committees, and quasi-governmental organizations. Fifty-seven percent of Federal health expenditures in 1979 were for services to the elderly.(10) Health expenditures for nursing homes alone were estimated at over $21 billion in 1980, and are projected to increase to over $75 billion by 1990 unless improved methods of prevention or treatment are developed for problems responsible for institutionalization.(11) There is evidence that dementia alone may account for as many as 50 percent of nursing home residents.(12)

Major Barriers/Issues Relating to Program Performance

Geriatric research must receive major emphasis in order to respond to the mandated responsibilities of NIA. A significant gap exists between those responsibilities and the research program summarized here. This program is quite new; some critical initiatives have only recently been activated; and major emphasis areas--nutrition, pharmacology, endocrinology, behavioral medicine, and biopsychology--are underdeveloped. In most areas, however, appropriate focal issues have been recognized, baseline data accumulated, and relevant hypotheses are being posed for testing.

More specifically, there is a shortage of investigator-initiated projects for research on health maintenance, such as urinary incontinence, decubitus ulcers, and infectious diseases. To encourage research in these and other areas, NIA has sponsored workshops to prepare specific program announcements. A program announcement on urinary incontinence has been prepared, and an RFA (Request for Application) on detrusor instability is being developed. A competitive contract for combined epidemiologic-diagnostic studies on incontinence in the elderly will be prepared. A workshop on infectious diseases in the elderly is scheduled for FY 1981 to be followed by a program announcement. A program announcement on decubitus ulcers has been drafted.

Research in geriatrics has been impeded by the sequestration of patients within nursing homes that are usually remote from academic medical centers.(13) To address this problem, NIA is developing a program to support the integration of nursing home residents into the geriatric research, medical education, and medical care functions of academic medical centers. An RFA (Request for Application) for this initiative is planned for FY 1982.

NIA is developing plans to initiate an epidemiological study to determine the incidence and risk factors associated with fractures of the hip in the elderly. A central objective is to evaluate the impact of race, education, and socioeconomic factors on the pathogenesis of osteoporosis, a condition reported to be substantially more common in white persons than in black.

Four contracts developed by the Epidemiology, Demography, and Biometry Program are in the initial stages of implementation and will expand greatly the knowledge base concerning risk factors, antecedents, and clinical management for specific medical problems that primarily affect the elderly. These studies will empasize noninstitutionalized subjects in urban and rural population groups. They should allow expansion of research into specific scientific issues by the research grant mechanism.

The behavioral science component of Geriatric Research is being expanded by encouraging research in the general area of intervention through psychological and biomedical mechansims to improve and extend the productivity and independence of the elderly. A program announcement to emphasize the interests of NIA will be released during FY 1982.

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11. Health Care Financing Review, 1980, p. 11, Health Care Financing Administration.

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Director's Overview

Disease prevention is a major focus of the research programs of the National Institute of Allergy and Infectious Diseases (NIAID). Prevention is one of the most cost-effective ways to deal with infections. Indeed, the annual savings in medical care cost that flow from the use of vaccines would fund the Institute's research for decades to come. While the prevention of allergies and immunologic diseases will require new modalities to manipulate the immune system, possible solutions are becoming increasingly available and need clinical validation.

National concern about the rising costs of health care emphasizes the need to examine new procedures for the prevention and treatment of infections and allergic diseases. Worldwide, infectious diseases, including parasitic infestations, are the leading causes of morbidity, disability, and death. In the United States, socioeconomic developments, antibiotics, and vaccines have reduced mortality, but infections remain a major cause of morbidity and health care cost. Patients with infectious diseases account for 20 to 30 percent of all patient visits to physicians' offices, and antibiotics are the most frequently prescribed drugs. Patients with allergies make at least 43 million visits each year to physicians at an estimated cost of over $1 billion dollars.

Simple solutions do not exist, and practical limitations on resources compel NIAID to establish priorities and emphasize those problems that appear most important or most amenable to an early solution using available technology.

The intellectual vigor of immunology as a discipline continues unabated and heavily supported by the Immunology, Allergic, and Immunologic Diseases Program. We are rapidly developing an understanding of the complicated interactions between body chemicals and the various cells that comprise the immune system. This system includes transactions between cells of the blood and lymphoid tissue--"T" & "B" lymphocytes, macrophages, mast cells--and the complex antibody proteins--IgG, IgA, IgM, IgD, and IgE. Interactions among cells and molecular elements lead to stimulation or suppression of immunity and of immunological memory. Biochemical mediators ranging from simple well-known substances, such as histamine, to much more complicated molecules of essentially unknown origin and structure, such as complement and the arachidonic acid system influence the immunological process.

The excitement derives also from the realization that many of the bodily changes in human disease--indeed what in many cases is the disease--are mediated through the immune system. Some kidney disorders, arthritis, diabetes, and systemic lupus erythematosis are diseases in which immunologic research may hold promise for prevention, therapy, and prediction of increased risk. The possibility of predicting increased risk of specific diseases is one of the interesting and far-ranging developments of immunogenetics. This branch of immunology started with cell typing for blood transfusions and progressed through transplantation research to the recognition of other histocompatibility antigens on cells or organs. We now recognize that the structure of genes determining the inheritance of histocompatibility is very complex and is better termed the "major histocompatibility complex" (MHC).

Other genes, such as immune response genes and immune-region-associated genes, are part of the MHC in man and animals. These appear not only to govern the immune responses of the body to foreign invaders, such as viruses, bacteria, and environmental pollutants; but also appear to be important in determining the development of self-destructive, autoimmune reactions and possibly tumor immunity. Psoriasis, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosis are examples of disease where the attack of the immune system on the body's own tissues plays a major role.

Work is in progress on the biochemical structure of specific and common antigens of bacteria and viruses. Special attention is given to new processes that yield an optimal form of antigen for immunization. Problems to be solved include stimulation of the immune system of the immature, correction of a defective system, or aiding the failing defenses of aging or immunologically inadequate patients. Two new biotechnologies, recombinant DNA methodology and monoclonal antibodies, have greatly expanded opportunities and resulted in major scientific excitement.

The Microbiology and Infectious Diseases Program is concerned with a wide variety of infectious agents--viruses, bacteria, fungi and parasites--which cause disease in all organ systems. Prevention of such diseases by vaccines is a central objective of the program, but the activities also include the discovery and development of antibiotics and antiviral substances for therapy. These applications depend upon basic research for the discovery and identification of new microbes; study of the mechanisms of growth, replication, and inheritance in viruses and bacteria; physical, biochemical and antigenic structure of infective agents; along with patterns and mechanisms of transmission, invasion, and resistance.

The Institute recognizes a set of well-defined infections that have high incidence and obvious major socioeconomic impact, including influenza, viral hepatitis, the sexually transmitted diseases, viral gastroenteritis, and nosocomial infections. While the research and development problems that will lead to effective prevention and control are formidable, the approaches to solutions are well recognized. In addition to these well-defined diseases, there are a series of other problem areas, including: latent infections, the infectious nature of chronic and degenerative conditions, innovative approaches to immunization, and the molecular biology of living organisms.

Farthest removed from immediate clinical applications are the basic studies of how living matter is organized structurally, how its mechanisms function, and how its heredity is passed on. For these studies bacteria and viruses have proved to be cheap, efficient model systems, sensitive probes to the structure and events at the molecular level, and directly applicable to approaching the medical problems of man. These basic, free-ranging research projects form the underlying scientific base for more applied projects that eventually result in improved prevention.

The Institute relies on free-ranging research in microbiology and immunology to obtain new knowledge needed to solve the health problems within its mission. The Institute planning process draws heavily on a series of task forces and study groups which, in aggregate, cover essentially all Institute responsibilities. The following have been active over the last several years: (1) Asthma and Other Allergic Diseases Task Force, (2) Virology Task Force, (3) Sexually Trasmitted Diseases Study Group, and (4) Study Group on Immunology. Their recommendations are considered by staff and Advisory Council members in planning budget and program changes.

Four major factors influence Institute program priorities: (1) the enormous number of allergic and infectious disease entities having public health importance; (2) the need to support a large variety of individual research grants to obtain fundamental knowledge required to solve many of the more pressing problems; (3) the limited budget available to support targeted developmental studies under contract; and (4) the lack of any other significant source of public or private support for certain research areas of current medical and political significance, such as allergies, sexually transmitted diseases, and tropical diseases.

Fiscal Year 1981

During the next decade, there will be major advances in the prevention, diagnosis, and treatment of infectious and immunologically mediated diseases. These advances will stem from:

- Commercial development of biologically active products using recombinant DNA technology.

- The use of lymphocyte hybridomas to produce monospecific antibodies and lymphokines to be employed as diagnostic reagents, as well as new medications for immunotherapy and antigen-specific vaccines.

- Recognition of internal events that modulate the interconnected individual components of the immune system and the ability to manipulate these events to regulate both beneficial and destructive aspects of immunity.

- Identification of the chemical structure of biologically active substances involved in the inflammatory response to infection or hypersensitivity, and synthesis of analogs to prevent or moderate the destructive elements of inflammation.

- Identification of the chemical structure of viruses and the processes by which they invade, replicate, and escape from the cell or are eclipsed into the latent state; and synthesis of antiviral drugs that will specifically interfere with one or more of these steps in virus multiplication.

- Identification of other factors that determine microbial pathogenicity in general and synthesis of special antimicrobial agents useful in the treatment of specific infectious processes.

Several current achievements illustrate the use of these advances to develop new opportunities in treatment and prevention:

- Recombinant DNA technology has been used in _in vitro_ bulk production of pure interferons.

- Investigators at NYU and Genentech, Inc., are discussing a possible agreement to use recombinant DNA and hybridoma technologies in producing an antimalarial vaccine derived from the sporozoite of human falciparum malaria.

- Recombinant DNA technology has been used to produce the surface antigen of hepatitis B virus in _E. coli_. A vaccine derived from surface antigen harvested from human serum is 90-95 percent effective in prevention of the disease in man. This may play an important role in our collaborative studies with NCI on the role of this infection in hepatic cell carcinomas.

- Cloned lymphocytes derived from a single parent cell have been cultivated _in vitro_. These cultivated clones are now employed to examine the genetic control, cell structure, and multiple functions of lymphocytes. Animal experiments with cloned lymphocytes suggest possible uses in new forms of immune therapy.

- Monoclonal antibodies have been produced commercially for use in research, clinical diagnostic, and other laboratory procedures.

FY 1982 Program Changes

Because this is essentially a no-growth budget, the NIH commitment to stabilize the base of investigator-initiated research grants severely limits our programmatic flexibility. We anticipate awarding only 420 competing regular research projects (an increase of 3 percent over FY 1981). Only 84 research and development contracts will be awarded in FY 1982, an increase of 5 over FY 1981. This number is insufficient to exploit the new opportunities for applied research. Research centers, training, and various K awards will all remain at or near the FY 1981 level, even though there are strong program needs for expansion.

The greatest impact may be in the intramural research program. The staff will remain at 493 positions, without meeting the needs of the Ambulatory Care Research Facility (ACRF). The intramural budget is less than a 10 percent increase over the FY 1981 budget. Recent data suggest that because of inflation, prices of equipment, materials, chemicals, and animals have grown about 25 percent per year over the past decade, an increase much higher than the inflation index usually employed to calculate research costs. The long term effect of this on intramural research is obvious.

No major program changes are planned during FY 1982. We will continue to support research in areas included in our previous portfolios. The only mechanism for funding new initiatives in this period of budgetary stringency is deferring or scaling down previously planned efforts. If this is done, a few high-priority projects can be started. Several have been strongly endorsed by the Advisory Council, study groups, and task forces:

- Increase the number of multidisciplinary Sexually Transmitted Diseases Centers to provide training experience for clinical investigators (a unique opportunity apparently exists in Puerto Rico).

- Emphasize molecular immunogenetic research to capitalize on the recent discovery of somatic gene rearrangement during lymphocyte differentiation, and other new discoveries concerning the interaction of subsets of lymphocytes and chemical mediators of immunity. New knowledge of the mechanisms of antibody diversity and MHC polymorphism (transplantation antigens) will be employed to examine immune regulation. The ultimate goals are new forms of therapy to prevent or treat infectious diseases and immune disorders.

- Focus attention on development of a few vaccines and expediting of clinical trials--e.g., gonococcus and group B streptococcus--as part of the HHS initiative on the Accelerated Development of New Vaccines.

- Identify, in the area of asthma and allergic diseases, allergic problems associated with industrial exposures. There are promising opportunities to develop drugs that will inhibit the action of inflammatory mediators activated by industrial compounds.

- Explore new approaches for development of vaccines against respiratory syncytical virus and rotavirus infections in children.

FY 1983 Program Changes

This level of funding would maintain programs at approximately the FY 1982 level and accommodate the following additional actions:

- Maintenance of most grant-supported program activities with a small increase in the number of grants (32 over FY 1982), but new grant program initiatives of any significant degree could not be undertaken.

- Pilot projects for the HHS initiatives could be started.

- Preliminary work on Federal-academic collaboration to develop new antiviral and antiallergic drugs could be started.

- Investigator-initiated research on the immunogenetics of transplantation and the regulation of lymphocytes will be augmented. New alternatives for the directed manipulation of the immune system will stem from the recognition of lymphocyte and lymphokine function, and the interaction of suppressor and helper cells and other active factors derived from cloned lymphocyte populations.

- Restoration of training awards to a number 10 percent above FY 1982 levels, and the addition of K01 and K08 awards to specifically enhance the supply of clinical investigators.

- A limited effort to meet critical needs within the immunology research programs for newly developed and sophisticated instrumentation such as cell sorters and amino acid sequenators.

- Vaccine trials would be expanded or initiated for group B meningococcus, H. influenzae, and varicella vaccines.

- Within the broad range of STD research, genital herpes research would be specifically augmented by expanded studies of its natural history, and treatment with new promising antiviral compounds.

- Research grant funds would be earmarked to emphasize the special interests related to international bilateral agreements, the urgency to develop parasitic vaccines, and an expansion of other projects in international research.

NIAID

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Institute of Allergy and Infectious Diseases

DATE: JAN 30 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It is clear that the knowledge base is developing rapidly in a number of areas of concern to the Institute, and with the technologies now available, this momentum should continue to offer opportunities to increase our understanding of the basic mechanisms of disease and enhance our ability to modulate these in beneficial ways. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

DS Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

The knowledge base in a number of areas of concern to NIAID is developing at an extraordinary pace. These include the recognition of internal events that modulate the interconnected individual components of the immune system and the ability to manipulate these events, the pathologic physiology in asthma and other allergic and immunologic diseases, the use of lymphocyte hybridomas, development of biologically active products using recombinant DNA technology, identification of the chemical structure of viruses and the process by which they invade, replicate, and escape from the cell, and synthesis of anti-viral drugs that will specifically interfere with one or more of these steps in virus multiplication.

Impact of Stabilization

- The number of program projects to be supported in 1981 and 1982 will remain nearly constant, although there is a need to increase support to provide for opportunities in the asthma and allergic diseases program area.

- The number of research and development contracts awarded in 1981 will drop substantially from 1980 levels; the 1982 planning assumption will allow only a modest increase over 1981. This has reduced and will continue to impair the Institute's ability to exploit new opportunities for applied research and development activities.

- Support for research centers and training in 1982 will essentially remain at 1981 levels, even though the need for program expansion is strong. Training has been far below optimal levels for the maintenance of manpower requirements in fields of interest.

- The most severe negative impact of the stabilization initiative will be on the intramural program. The number of positions will remain the same in 1982 and not meet the needs of the ACRF. The slight increase in funds will not be adequate to offset inflation.

- No major program changes are planned for 1982.

Opportunities

With the rapidly expanding knowledge base, there are many opportunities for new initiatives. Most of these initiatives have strong endorsement by the

Advisory Council, study groups, and task forces, but plans must be either scaled down or deferred, given current budget constraints. If increases become available in FY 1983, some of the opportunities which would be pursued include:

- Increasing the number of multidisciplinary Sexually Transmitted Disease Centers to provide training experience for clinical investigators.
- Further development of the recently established hybridoma bank.
- Major expansion of investigator-initiated research projects in immunology and microbiology.
- Expanded training programs for epidemiologists and clinical investigators in asthma and allergic diseases and the molecular and clinical virology program areas, as well as further development of research centers in these areas.
- Accelerated development of vaccines. An integral part of this HHS health research initiative is a proposal to establish an interagency working group to develop a technical plan for the development of each individual vaccine through phase III trials, to monitor the progress of the development of each vaccine, and to decide what priority should be given to each vaccine in the plan if there is a shortfall of funds.
- Expansion of clinical immunology, clinical immunoregulation, immunopharmacology, and basic and applied immunogenetics, including transplantation, through the application of recombinant DNA and hybridoma cell fusion technologies.

Developmental Activities

The Institute has proposed three major joint Federal, academic and industrial programs, all predicated on a significant increase in funding, as follows:

- De novo Development of Antiviral and Antiallergic Drugs. This program would focus on the development of those pharmacologic agents that will inhibit the penetration, replication and release of viruses from the human cell and those targeted at preventing the release or function of the principal biomedical mediators of asthma, allergies, and other immunologically associated inflammations.
- Serological Reagents Needed for Basic Research and Prevention, Diagnosis, and Treatment of Disease. The purpose of this effort would be to develop a program which would make available to industry the technology needed to produce useful monoclonal antibodies in quantity and determine the range of beneficial research and clinical uses.
- Pharmaceuticals for Developing Countries. The purpose of this program would be to develop new low cost drugs against major parasitic diseases

that affect a high percentage of the populations of the developing countries but are uncommon in the United States.

Discussion of possible approaches to stimulate the private sector to pick up the development costs in some of these activities centered on the Institute's experience with the development of hepatitis B vaccine, where the Institute conducted and supported the basic research and development and testing in the animal model. Industry is now engaged in the clinical testing and production of the vaccine.

Action Items

The Institute is providing information to the Associate Director for Program Planning and Evaluation which describes the development of the hepatitis B vaccine and the roles played in this effort by the Federal Government, academic community, and the private sector. This information will serve as the basis for an agenda item at the March 1981 DAC meeting.

The Institute has provided a brief listing of all current repositories and resource banks it supports.

NIAID

Sexually Transmitted Diseases

Statement of Issue

Sexually transmitted diseases have increased explosively in prevalence during the past decade. Gonorrhea and non-gonococcal urethritis are at epidemic levels, as are sequelae such as pelvic inflammatory disease. Of special note is herpes genitalis caused by Herpes Simplex Type 2 virus; over 300,000 new cases are estimated to occur annually. Many of these persist as chronic, painful infections that interfere with sexual activity and pose a serious infectious threat to newborn infants. Inability to meet demands for increased research opportunities will bring societal reaction.

Discussion of Issue

During the past year, the NIAID-supported Study Group on Sexually Transmitted Diseases completed its report and recommendations. The report and recommendations were endorsed, reprinted, and widely distributed by the American Social Hygiene Association.

The NIAID Advisory Council reviewed and endorsed the report. It reduced recommendations on funding in recognition of overlapping recommendations from other Task Force reports and responsibilities of other Institutes. In particular, it reduced the recommendation for research on genital herpes in FY 1985 from the $13.5 million recommended by the Study Group to $4 million.

This Council recommendation has brought a flood of letters from all over the United States, protesting any lack of full effort to solve a chronic socially, mentally, and physically disabling disease that is highly prevalent among the young. We expect this correspondence to be reflected at the House hearings.

Alternatives and/or Suggested Position

The NIAID will include a report on the Study Group Report on Sexually Transmitted Diseases and on the recommendations of the NIAID Council in its opening statement. The NIAID will also be prepared to answer questions. It is suggested we provide you with a less than one-page briefing document related to the NIAID testimony when it is completed.

It should be noted that accelerated development of several vaccines for STD were included in the NIAID-proposed initiative. If the initiative were funded, it would largely allay some of the concerns about our efforts on herpes genitalis, gonorrhea, and pelvic inflammatory disease.

International Medical Research

Statement of Issue

The proliferation of international agreements for medical research has been unaccompanied by either resources or administrative and political recognition.

Discussion of Issue

The NIAID has responsibility for the U.S.-Japan Cooperative Medical Sciences Program. This program has been broadened by adding viral hepatitis and immunology, with requirements for additional consultants, travel, and other costs. We are also involved in the U.S.-China, U.S.-U.S.S.R., U.S.-Egypt, and U.S.-India health agreements. We are identified in the OSTP "other" U.S.-Japan Program in the subject areas of immunology and recombinant DNA research and development. All of these initiatives have imposed drains on resources in addition to the existing large program in international medical research amounting to about 12 percent of the NIAID total appropriation. Still further demands are being generated in Africa and Latin America by the expectations of medical groups in those countries that see advantages in such agreements. It is difficult to carefully consider all responsibilities and requirements for all of these agreements in the budget allocation process.

Alternatives and/or Suggested Position

The NIH should consider a study of its role in international medical research. This could serve as the first step in seeking fuller recognition of resources required to meet obligations and opportunities in this important area.

Impact of Budget on Applied Research

Statement of Issue

In development of the FY 1982 budget, the constraints that reduced funds for applied research and development (contracts, and now, cooperative agreements) persist. The reduced contract budget was only sufficient to meet necessary commitments. Continuation of this situation poses special problems for the logical progression of NIAID research activities.

Discussion of Issue

The ability of NIAID to focus on practical application of research results requires programs supported by contracts. These program efforts (e.g., sexually transmitted diseases, influenza, viral hepatitis, bacterial vaccines, antiviral substances, viral respiratory diseases) represent Institute-directed research on infectious diseases with a major impact on health in the United States. The purpose of research contracts is to move new knowledge acquired through basic research toward clinical use. Representative of contractual activities are: clinical trials, animal colonies and facilities, reagent acquisition, vaccine production, epidemiologic surveys, and stimulation of basic research where "gap" areas may exist.

Scientific advances in vaccine and antiviral development have brought forth the need for increased targeted research activities, but funds to support these activities have not been increasing. For example:

NIAID

Fiscal year	NIAID R&D contract dollars (dollars in thousands)	Cumulative % reduction adjusted for inflation	Contracts as % of extramural funds
1978	$16,240	-	14
1979	15,679	- 10.8	11
1980	15,253	- 18.9	9
1981 est.	14,935	- 29.3	8

The benefits of directed research can be measured and the cost benefit calculated. Examples of recent successes from directed research include: demonstrated efficacy for adenine arabinoside for herpes encephalitis, with FDA licensing for this application; efficacy in treatment of neonatal herpes, and successful completion of a therapeutic trial for "shingles." Successes with other antiviral drugs such as amantadine and interferon have been accomplished. Contract research has been instrumental in demonstrating effectiveness of vaccines against bacterial pneumonia and meningitis. These two vaccines are now licensed. Directed research has contributed extensively to development and successful evaluation of inactivated hepatitis B vaccines, as well as attentuated and inactivated vaccines for influenza.

Alternatives and/or Suggested Position

It must be stressed that directed research is the most efficient way to utilize many of the new technologies emanating from investigator-initiated basic research. Once a particular area has been highlighted for Institute efforts, support should be adequate to ensure an adequate and stable level of work. Like basic research, targeted research will yield an end-product only if support is constant. With current trends of reducing contract funds, technology transfer to physicians and the public could be in jeopardy.

Interferon

Statement of Issue

Because of increased interest in interferon (IFN), NCI funding was increased in FY 1979 and 1980 to carry out clinical evaluations of IFN against cancer therapy. The dominant role, past and present, of NIAID in the development and use of IFN as an antiviral has been recognized, but not to the point of increasing NIAID funds. Congress has requested annual statements from NIH on collaboration between NCI and NIAID in IFN research. NIAID has not been able to increase its effort even though new technology has opened up new opportunities.

Discussion of Issue

Until FY 1980, NIAID was the principal U.S. Governmental supporter of IFN research. Its efforts began shortly after the discovery of IFN by Alick Issaacs in 1957, when the Institute sent an intramural scientist to England to work with him. Research on its role in infectious disease and the development of a promising inducer of IFNs has continued in NIAID intramural laboratories. Since the late 1950s, NIAID extramural programs have supported and continue to support most of the grants in this field. In 1969, NIAID decided that the time was propitious for the initiation of a targeted program to determine the clinical potential of IFN and other antiviral drugs.

Considerable information has been obtained on the antiviral aspects of IFN, its production, mechanism of action, pharmacology, toxicology and early studies on clinical efficacy in virus infections. These studies formed the groundwork for studies in cancer patients. IFN production efforts of Dr. Kari Cantell in Finland have been largely supported by NIAID through purchases of material used in clinical studies. The discovery of several types of IFN with different biological properties is a direct result of NIAID-sponsored research and distribution of standard reagents. The role of NIAID is internationally recognized by the designation of the Development and Applications Branch as the WHO National Interferon Centre for the United States.

The increased publicity on IFN has resulted in two specific problems. The first concerns the over-promise of a potential miracle drug against cancer. In proper perspective, IFN may prove to be of some clinical value in treatment of cancer as well as infectious diseases, but it is not a miracle drug. The second problem stems from the first. Because of the emphasis as an anti-cancer agent and increased funding in NCI, attention has been directed away from research in the use of IFN to treat virus infections.

Alternatives and/or Suggested Position

IFN research is at an important crossroads. Recombinant DNA techniques are making IFN more available for clinical evaluation and unfolding new information on the genetic content of production of the multiple products and the structure of these products. There is a great need for increased research on the various properties of IFN, particularly on the immune regulatory functions and additional clinical studies in viral diseases such as rabies and chronic infections (hepatitis B, SSPE, Jakob-Creutzfeldt disease, multiple sclerosis, etc.). Currently there is some collaboration between the NCI and NIAID in development of reagents and an IFN inducer. If the potential of IFN is to be realized and Congressional expectations met, expanded research is needed by NIAID which will require an increase in the Institute budget, particularly for directed research.

Equipment for Immunologic Research

Statement of Issue

Equipment needs for a modern laboratory at the forefront of immunologic research have rapidly escalated in sophistication and cost. A new system of equipment grants is needed.

Discussion of Issue

There is a continuous process for the development of more sophisticated, sensitive, and powerful equipment needed in basic immunologic and microbiologic research if a laboratory is to maintain its leadership position.

The NIAID Study Group on Immunology Report, soon to be published, summarizes this issue and shows the development of automated protein sequenators from 1967 with the Caltech gas phase solid-state instrument of 1980 being 10,000 times more sensitive than the Edman-Begg instrument of 1967. The new instrument is also faster and uses fewer reagents. Other automated instruments in development that will extend the capabilities of laboratories and accelerate data collection are the DNA synthesizer, gene analyzer, and high sensitivity mass spectrometer.

One intramural scientist estimates that a highly productive research laboratory will need the following, over and above the usual array of equipment:

Protein sequenator instrument array	$250,000
Cytofluorograph	200,000
Gas chromatograph mass spectrometer	250,000
Peptide synethesizer (and services)	100,000
	$800,000

He knows of few instances of successfully shared instruments or centrally managed instrument facilities. In the latter, the instruments are not properly maintained and calibrated. In the former, demands exceed capabilities. Our projection is that equipment funds of up to $1 million each could be well used by 20 to 30 institutions.

This is a generic problem for the NIH, the National Science Foundation and other granting agencies. Most highly sophisticated laboratories depend on multiple sources of support.

Alternatives and/or Suggested Position

The NIH should move immediately to consider approaches to deal with this issue.

PROGRAM PERFORMANCE SUMMARY

ACCELERATED DEVELOPMENT OF NEW VACCINES PROGRAM

Program Description

This NIAID program is a component of a Departmental Initiative(1) for the Accelerated Development of New Vaccines. These initiatives focus upon selected problem areas where important mission needs of several HHS agencies coincide with significant scientific opportunity. For these areas, they represent efforts to strengthen research through cooperative planning and information exchange on a continuing basis. The purpose of this initiative is to develop a clearly identified, recognized, and coordinated approach to the further conquest of vaccine-preventable diseases. The knowledge and technologies which have been emerging from basic research now provide new opportunities to solve problems that have been insoluble with earlier technology and knowledge. The incentive for expanded efforts lies in recombinant DNA and hybridoma technologies and in the better understanding of the workings of the immune system. Such new knowledge will permit radically different approaches to the problems of immunization. The goal of the initiative is to expedite the availability of needed vaccines, and its essence is the selection of a few candidate vaccines for intense effort with additional funding so as to bring these vaccines into use at least several years earlier than might otherwise have been the case.

An expanded initiative on development and subsequent use of new and improved vaccines supports the HHS policy to emphasize prevention. HHS has published two reports(2,3) on Health Promotion and Disease Prevention that highlight the limitations of what can be done with existing knowledge and technology; therefore, the base has been laid for increasing the capability in disease prevention. As measles, poliomyelitis, diphtheria, and pertussis vaccines have so clearly shown, immunization offers a most cost-effective means of control. With new technology promising the capability to solve problems that have prevented progress in the past, a definitive program to exploit this opportunity is needed. Industry is making large investments in recombinant DNA and hybridoma technologies, some of which are directed at vaccines, and establishment of a program on new vaccines should further encourage such efforts on the part of industry.

Infectious diseases constitute major problems for U.S. health authorities and citizens because of high morbidity, medical costs, interference with education and productivity, and crippling complications. HHS(2) estimates that infectious diseases cause at least 156 million lost work days each year and that the costs for treatment and lost productivity are $24 billion annually. Some 291 million illnesses due to infection were estimated to have occurred in 1975. Other significant statistics are:

- Sexually transmitted diseases (STD). In 1977, 10 million cases in the United States, 86 percent in 15- to 29-year-olds. The 10 million included 2.5 million cases of gonorrhea (4.5 percent of 8.7 million women from all socioeconomic levels tested in 1979 had positive cultures); 2.5 million cases of chlamydial or mycoplasmal genital infections; 0.5 million cases of genital herpes; sterility in 100,000 young women as a complication of STD each year (pelvic inflammatory disease); 50,000 babies born with STD annually, of which 8,000 will die in a few days and 8,000 more will develop residual brain damage.

- One quarter of all visits to a physician each year caused by infection. Antibiotics are the most frequently prescribed drugs.

- Bacterial meningitis afflicts about 20,000 each year, mostly children under age two, with 10 to 15 percent death rate. Brain damage occurs in a large percentage of survivors. Group B streptococcus infections are a primary cause in the first three months of life, and *Hemophilus influenzae* b is the principal cause between ages six months and two years.

- Epidemic respiratory syncytial virus infections occur in infants under one year, and are a major cause of hospitalization and mortality at that age. Also, these virus infections are a major cause of nosocomial epidemics in patients and staff of pediatric hospitals. At least 60 percent of children have had one RS infection by the age of two.

- Pulmonary infection caused by *Pseudomonas aeruginosa* is the major cause of death in individuals with cystic fibrosis. Treatment has been only moderately successful, and means for prevention of bronchial colonization by these organisms must be sought.

- Rotaviruses are a worldwide major cause of severe dehydrating diarrhea in very young children. In the U.S. 60 to 70 percent are infected in the first two years of life. In developing countries this infection is a major cause of infant death.

If HHS fully implements the initiative and designates a series of vaccines considered to be of high priority for HHS developmental efforts, several component agencies would respond within the general areas of their mission. NIAID has long been considered to have the lead role in research leading to new vaccines and in demonstrating the feasibility of a new product. It would serve as the sponsoring Institute and provide the Initiative Coordinator from among its senior staff. The National Institute of Dental Research would have a special role related to caries and other oral dental problems; the National Institute of Child Health and Human Development would collaborate in the investigation of candidate vaccines in infants, very young children, and mothers. The National Eye Institute would identify populations suitable for investigational use of vaccines against eye infections and take the lead in planning such studies; and the National Cancer Institute would continue its efforts in vaccine studies against hepatoma. The Centers for Disease Control has the primary role of surveillance and investigations of disease outbreaks and for application of vaccines for disease control. It would play a key role in efficacy testing and surveillance for adverse effects. The Bureau of Biologics/Food and Drug Administration has the responsibility for the control of investigational new vaccines in humans, and for licensing. It would play a key role in defining the properties of a vaccine, in monitoring investigational use, in the development of tests for potency, and in the study of reactions. The pharmaceutical industry must be brought into new vaccine efforts early, since the eventual preparation and distribution of a licensed vaccine depends on industry.

In this collaboration, each participating agency retains responsibility for the quality of the science and program relevance of the activities it supports. Therefore, this Program Performance Summary will be concerned primarily with NIAID efforts and those HHS activities that directly impact on the Institute.

The NIAID program contains projects directed at all necessary aspects of vaccine development from fundamental studies on the etiologic agents through identification of the immunogenic antigens to developmental studies on vaccine production.

Major emphasis is being placed on development of new vaccines against:

- Gonococcal infections
- Genital infections caused by chlamydiae and mycoplasmas
- Bacterial meningitis, particularly _H. influenzae_ b infection
- _P. aeruginosa_ infection in cystic fibrosis victims
- Hepatitis B and nonA-nonB hepatitis virus infections
- Infantile bronchiolitis (respiratory syncytial viruses)
- Parainfluenza virus respiratory infections (croup)
- Infantile diarrhea (rotaviruses)
- Genital and oral herpes simplex infections.

Efforts are also being made to improve pertussis vaccine by reducing the frequency and severity of side effects following injection.

Legislative History

This program is not mandated by specific legislation but is part of the mission of the NIAID under the authority of the Omnibus Medical Research Act (P.L. 81-692, 64 Stat.L.443). The Institute's mission is to conduct and support research contributing to a better understanding of the causes of allergic, immunologic, and infectious diseases and to develop better means of preventing, diagnosing, and treating illnesses. Institute-supported research has furthered these general goals and the development of various specific vaccines for more than 20 years at a significant level.

Congressional appropriation committees were informed of this new accelerated endeavor by NIAID during the FY 1982 hearings and the continuing interest of these bodies in more effective disease prevention was evident through the various questions raised during the hearing process.

Funding History

Budget for Accelerated Development of
New Vaccines Program, FY 1978-82 Est.
(In Thousands of Dollars)

	1978	1979	1980	1981	1982(Est.)
Research Grants					
Research Project Grants	$1,349	$2,199	$3,032	$4,179	$4,387
Research Centers	0	0	0	0	0
Other Research	77	0	38	0	0
Research Training	48	47	67	62	65
Research Contracts	700	846	1,066	718	754
Intramural Research	1,631	1,716	1,841	1,933	2,030
TOTAL	$3,805*	$4,808*	$6,044*	$6,892*	$7,236*

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*These grants and contracts support highly targeted efforts. A much larger effort in basic research sustains this ongoing initiative to develop new vaccines.

In FY 1980 there were 12 senior professionals from the NIAID staff who were directly involved with this program either as Health Science Administrators or as Principal Investigators for Intramural Research Projects. It should be emphasized that in addition to the technical support of research, the review and administration of grants and contracts, site visits, program planning and evaluation functions, and management of clinical trials all require considerable additional staff. We estimate that 70 staff persons were involved with this program in some capacity.

Program Objectives and Activities

The programmatic goal is to exploit new technologies and bring a selected group of vaccines into use earlier than might otherwise be the case. The management objectives are to coordinate the relevant components of the National Institutes of Health, the Centers for Disease Control, and the Bureau of Biologics/Food and Drug Administration so as to develop within the HHS mechanisms for assigning priorities for vaccine development. These mechanisms will include reviews by workshops of the "state-of-the-art," interactions with industry, assessment by advisory committees and consultants, and determination of the cost/benefits of vaccines considered desirable because of socioeconomic and medical needs. All of these elements will enter into the construction of a list of vaccines in priority order which will then be used to encourage accelerated research development through grant, contract and intramural research and development mechanisms. These activities are measurable in terms of: 1) meetings of interagency groups; 2) recommendations of advisory committees and workshops; 3) evaluation by consultants; and 4) continuing assessment by NIAID staff and the resultant requests for applications or proposals. The ultimate measure will be the number of new vaccines brought into use.

In order for the NIAID program to be fully effective and integrated with other components, a different kind of interagency management group must be established within HHS for this initiative. This must be a group of technically competent professionals with expertise in all aspects of vaccine development and testing who are intimately involved in the efforts of their respective agencies on the initiative. They must have extensive contacts in academic and international circles and in government and industry; must keep current on progress in vaccine development under auspices other than HHS; and must be able to take advantage of all new technical advances. The team would have the following responsibilities:

- Develop a technical plan for the development of each individual vaccine through Phase III efficacy trials;
- Monitor the progress of development of each vaccine, identifying obstacles as these arise, seeking solutions, altering technical plans as needed;
- Decide when development is stalled and cannot progress without new technology;
- Decide when technological progress makes development of still other vaccines possible;
- Decide what priority should be given to each vaccine plan if funds are inadequate for the whole; and
- Decide when the HHS initiative on a vaccine can be phased out as and if industry assumes primary responsibility.

The team will be chaired by the coordinator of the initiative and meet every three months. After each meeting, the team will prepare a progress report, proposing and recommending any action necessary by departmental or agency officials, recommending deletion of vaccines on the initial list, and incorporation of other vaccines in the list. Problems with funding or staffing that retard the effort would be identified in these reports. Copies of the reports would go to ASH (designated office); the Directors of NIH and CDC; the Commissioner of Food and Drugs; and the Directors of NIAID, NIDR, NICHD, NEI, NCI, and BOB/FDA. The initial report would append the development plans, projected timetable, and estimated costs for each vaccine. This would be updated annually.

Current Program Activity

NIAID-supported studies are now in progress on 16 vaccine antigens for six different bacterial and viral diseases that are relevant to this program; the majority of these studies are supported by investigator-initiated research grants. With intramural and contract-supported research, NIAID has encouraged the development of live, attenuated, respiratory syncytial, rotavirus and varicella virus vaccines and inactivated hepatitis B virus vaccine. Proposals in response to a contract solicitation are under review for studies on a recently identified parainfluenza virus antigen. Current work on bacterial diseases emphasizes development of vaccines for *H. influenzae*, type b, meningitis in young children, and gonorrhea.

The Institute supports five vaccine evaluation centers to assure access to selected pediatric and adult populations and one Center for Vaccine Development for infectivity and challenge studies in hospitalized volunteers. These facilitate the early human testing that must precede large-scale field trials.

Illustrative of the continual development of new data and information, the following recent advances are cited:

A phenomenon related to new approaches to immunization is that of bacterial adherence to mucosal surfaces, an aspect of bacterial pathogenicity that has received increasing attention in recent years. A number of investigators have now shown that the ability of certain bacteria to adhere to epithelial cells in vitro parallels their ability to produce infections in vivo. The premise of these studies is that the adherence of bacteria to tissue surfaces involves specific interactions between molecular ligands, referred to as adhesins, on the surface of the bacteria with specific structures, referred to as receptors, on the tissue surface. It is anticipated that the isolation and identification of the adhesin and receptor materials from each of these interacting surfaces will provide new approaches to the prevention of bacterial infections. In the case of the chemical component or attachment organelle that serves as the specific bacterial adhesin, vaccination using the purified adhesin as an antigen may produce immune responses resulting in the local mucosal secretion of anti-adhesin antibody.

Among the anti-adhesin vaccines, one of great current interest is that prepared from gonococcal pili. Two groups of investigators have now initiated early human trials of gonococcal pili vaccines, having demonstrated immune responses to the purified antigens. Prevention of adhesion alone may not suffice, however, and it may be necessary to combine pili antigens with outer membrane antigens that have been shown to promote opsonization. Further, gonococcal "toxins" may be involved. While assessing the relative virulence of piliated and non-piliated gonococci in organ cultures of human fallopian tubes, scientists have observed that piliated gonococci were more destructive than non-piliated ones. The damage to the ciliated mucosal cells was mediated by a subcellular toxic factor(s) identified as gonococcal lipopolysaccharide (LPS). Here, then, is another example of attachment facilitating delivery of toxin to target areas. To determine how many pili types must be included in a vaccine, and whether or not they must be combined with membrane antigens without LPS, will require extensive study. The recent appearance of strains of gonococci resistant to both penicillin and spectinomycin has given added impetus to the need to accelerate such research.

The inactivated surface antigen vaccine for hepatitis B developed by Merck Sharp and Dohme has been shown to be highly efficacious in male homosexuals, and U.S. licensure is imminent. (Licensed by FDA on November 16, 1981.) A similar vaccine developed at NIAID has been shown to be safe and highly antigenic. A trial in China where maternal HBsAg carrier rates are high is planned to test the efficacy of this vaccine in preventing neonatal transmission. A French-made vaccine has been effective in Senegalese children, reducing the incidence of the HBsAg carrier state of 85 percent in susceptible children at the 12th month of followup. Anti-HBs antibody of maternal origin did not interfere with active immunization, so vaccine can be administered soon after birth. If, as is strongly suggested by epidemiological data, chronic hepatitis B virus infection is a prelude to hepatic cell carcinoma (hepatoma), prevention of infection early in life should prevent virus-related hepatoma later in life. Liver cancer (presumably primary) is the third most important cause of death due to cancer in China, accounting for 15 percent of all cancer deaths.

A vaccine made by combining H. influenzae type b polyribose phosphate with a small amount (approximately 1/6 of the childhood dose) of inactivated pertussis cells has been made by the Lederle Laboratories. Preliminary studies indicate that this complex is antigenic in children under six months of age when given in three doses. It is assumed that protein conjugation converts the polysaccharide from a T-cell independent to a T-cell dependent immunogen. The NIAID wishes to collaborate with the manfacturer in an efficacy trial in Alaskan Eskimo populations with a high incidence of meningitis. In the United States, there are approximately 15,000 cases each year, and 10 to 35 percent of the strains are now resistant to ampicillin.

Evidence of Program Performance

Monitoring Program Performance

The NIAID supports relevant projects within this program through grant, contract, and intramural research mechanisms. Each mechanism results in a different approach to monitoring, in a strict sense, but all are followed for significant advances by a common approach. The Institute's staff responsible for the major program areas are Health Scientist Administrators who are scientifically trained and who monitor various areas of science as a routine part of their job responsibility.

Research grants are awarded to scientists who have submitted meritorious applications describing a research plan of their own design. The predominant portion of NIAID research grants are made in response to these investigator-initiated research applications. The Institute does, however, issue Requests for Applications to ensure that adequate emphasis is given to a few selected areas of research. Following award of a research grant, progress is monitored by a Health Scientist Administrator responsible for the specific program area. Progress is monitored via annual progress reports, receipt of scientific publications supported by the grant, interaction with the investigators at scientific meetings, and occasionally by visits to the investigator's institution.

Research Contracts are awarded following specific solicitations by NIAID for proposals to perform Institute-selected projects. Progress is monitored by Health Scientist Administrators responsible for the specific program areas. Progress is monitored by written progress reports submitted at frequent intervals, receipt of scientific publications, site visits, and interaction with the investigators at scientific meetings.

Component projects from the intramural research program are constantly monitored by the Laboratory Chiefs and the Office of the Scientific Director, NIAID, and subjected to periodic review by the Board of Scientific Counselors, NIAID.

The Program Coordinator has additional opportunities to monitor progress of the component projects and assess the significance of results for the total program. These opportunities are provided by his capacity to utilize individual consultants, advisory committees, workshops and task forces to review the research, assess progress, and recommend action. A major and important area to be monitored is research relevant to the program but not supported by HHS; this will require oversight of research activities in the United States and several active foreign countries.

Direct Evidence

The ultimate measure of the effectiveness of this program will be the number of new vaccines brought into use. Although this initiative has not yet resulted in any new vaccines being licensed, scientific progress has been made in several areas and significant advances have been made with several vaccines; examples are the recent success in trials of an industry-supported hepatitis B vaccine, growth of human rotavirus isolates in tissue culture, and the improved purification of antigens from Bordetella pertussis. (The hepatitis B vaccine was licensed by FDA on November 16, 1981.)

There are many precursors to successful immunization from the first step of identification of a clinical disease entity which can be segregated from similar syndromes by specific diagnostic procedures through eventual production of effective vaccines.

Once the vaccine is available for administration to the population for which it was developed, large-scale field trials are designed to test its acceptability, safety, and efficacy. Should it live up to the expectations, the new vaccine will find its place in medical practice, providing that both the medical profession and the public have been educated as to its benefits and limitations.

Assessment of progress from selection of a vaccine for accelerated development to eventual licensure can be measured by recording movement along the steps in the process. Although these steps are complex, difficult, and time-consuming, they may be outlined:

1. Understanding the disease and the host

    a. Clinical recognition
    b. Specific diagnosis
    c. Natural history
    d. Epidemiology
    e. Pathogenesis
    f. Resistance modifiers
    g. Nature and duration of immunity

2. Understanding the pathogen

    a. Specific identification and characterization
    b. Cultivation
    c. Antigenic analysis
    d. Genetic determinants
    c. Infection of other species; animal models
    d. Properties

        (1) Determinants of infectivity
        (2) Determinants of virulence
        (3) Determinants of antigenicity
        (4) Determinants of immunogenicity

3. Construction of an inactivated vaccine

    a. Optimum growth of pathogen
    b. Identification of essential immunogen
    c. Purification of essential immunogen
    d. Production of antigen using recombinant DNA technology
    e. Artificial synthesis of antigen
    f. Selection of adjuvants, if necessary
    g. Demonstrated antigenicity
    h. Production of pilot lots

4. Construction of a live, attenuated vaccine

    a. Growth in acceptable cells, tissues, or other cultures
    b. Satisfactory infectivity and antigenicity
    c. Demonstrated lack of virulence
    d. Demonstrated genetic stability (lack of reversion)
    e. Production of pilot lots

5. Testing the vaccines

    a. Inactivated

        (1) Early Phase 1 trials in humans
        (2) Challenge of immunized volunteers
        (3) Expanded trials to test reactogenicity and antigenicity
        (4) Final test of safety and efficacy in open field trials in populations at high risk

    b. Live, attentuated

        (1) Early trials in humans, isolated if necessary. Stepwise Phase 1 trials of attenuated vaccine from adults with antibody to children without antibody.
        (2) Challenge of immunized volunteers
        (3) Expanded trials to test antigenicity and transmissibility in semiclosed populations
        (4) Efficacy trials

            (a) By direct challenge of volunteers
            (b) By natural challenge of open populations

6. Production of commercial lots (not a primary function of NIAID)

7. Licensure (not a primary function of NIAID)

8. Professional and public acceptance

For each vaccine selected, a flow chart can be constructed using these development steps. But any systematic approach is complicated by the fact that certain vaccines may require multiple serotypes (e.g., rotaviruses) with each type, in effect, being a separate vaccine. Most bacteria and viruses will fall between steps 2.d and 3.c. Some, for example, non-A non-B hepatitis, are still at 1.a. Two protein conjugated polysaccharide vaccines (meningococcus group B, and H. influenzae, type b), are at step 4.a.(4) Inevitably, new discoveries will alter the course of events, and the program must be flexible and responsive enough to adjust to them. Nevertheless, for each vaccine under development, a system of steps can be used to quantitate progress.

Suggestive Evidence

The Institute draws heavily on a series of task forces and study groups which review large areas of science within our areas of interest. The task forces and study groups that have been active over the last several years include the following:

- Asthma and Other Allergic Diseases Task Force
- Virology Task Force
- Sexually Transmitted Diseases Study Group
- Study Group on Immunology

Institute initiatives stem from these task force-study group reports and ensuing Advisory Council recommendations. The following are examples of this process that relate to this program.

During the period of October 1976 through September 1978, the NIAID Task Force on Virology undertook an in-depth and comprehensive assessment of the state-of-the-art of virology, identifying several key areas of scientific opportunity.(4) The Advisory Council reviewed the task force report and recommended that the NIAID seek to double its investment in virus research over the next five years, expanding and emphasizing its efforts in 11 research areas. The research areas identified for expansion and emphasis included live virus vaccines and new and improved inactivated virus vaccines; new techniques for detecting, isolating, and propagating viruses; and virus structure, multiplication, and use as research models.

The Microbiology and Infectious Diseases Program was, in fact, sponsoring research in all of the 11 areas covered by the Advisory Council recommendations. Program emphasis was, however, shifted in accord with the Council's recommendations. In addition, the Task Force on Virology report provided essential background material for the NIAID Sexually Transmitted Disease Study Group recommendations on herpes simplex virus, cytomegalovirus, and hepatitis B virus infections.

The NIAID also participates in two interagency groups that have a significant influence on several components of the virology research programs. The Interagency Work Group on Influenza is composed of representatives from the NIAID, BoB/FDA, and CDC, which serves as the lead agency. The group is charged with developing an influenza pandemic contingency plan that includes an annual determination of new variants, the likelihood of epidemic or pandemic potential, establishing the vaccine formulation, and decisions regarding field testing. A second activity concerns the Interagency Group to Monitor Vaccine Development, Production, and Usage and is involved with vaccines other than those for influenza. This latter group is composed of representatives of the NIAID, BoB/FDA, CDC, and the military, and is responsible for monitoring the development, production, and supply of vaccines in the United States.

The Study Group on Sexually Transmitted Diseases (STD) was established in FY 1980, partly in response to Congressional interest. This group actively examined current research on sexually transmitted diseases.(5) A subcommittee of the Advisory Council formulated recommendations to be considered by the full Advisory Council at both the May and September 1980 Advisory Council meetings. In September of 1980 the Advisory Council recommended that NIAID increase its support for research on genital herpes and cytomegalovirus and reaffirmed their initial view that a substantial increase in the training effort was essential to the development of a high quality research program in sexually transmitted diseases. As a result of these recommendations, there has been a substantial increase in research funding in the overall STD program--particularly for: chlamydia, gonorrhea, herpes, and cytomegalovirus.

Current Assessment Studies

None.

Proposed Assessment Studies

A study has been designed and is being solicited via an RFP (Request for Proposal) for a program performance evaluation of the NIAID Vaccine Development Program. This study will provide the mechanism for reviewing research related to these vaccines and evaluating other important aspects of the program. It will provide the data base and recommendations for the programmatic/managerial selection of those specific vaccines most amenable to successful early development and clinical usage and that show promise for significant health improvements and reduction of the socioeconomic impact of the disease.

Vaccines will be examined and ranked following careful evaluation of the importance of the following measures as they pertain to the development of each specific vaccine.

- Adequacy of the science and technology base
- Significance of the socioeconomic impact of the disease: cost-effectiveness and cost-benefit estimates primarily for the U.S. but secondarily in developing countries

- Ethical and societal concerns regarding the specific disease
- Potential for safety and efficacy testing of the vaccine: epidemiological, ethical, and cost issues and access to target populations
- Acceptability and receptivity of physician/public
- Potential for industrial efforts, interest, and production feasibility

The study will be executed in phases, and three different categories of infectious diseases will be encompassed in a sequential, incrementally funded study, each phase estimated to require 10-14 months.

Phase 1. Review of those diseases for which safe, effective vaccines do not now exist but which result in high morbidity, mortality, or socioeconomic costs in the U.S. population in general (such as sexually transmitted diseases, including herpes type 2 and cytomegalovirus; acute bacterial and viral respiratory diseases other than influenza; acute virus diarrheal diseases; and other herpes simplex virus infections, such as herpes simplex type 1 and varicella).

Phase 2. Review of diseases of importance to special subsets of the U.S. population, such as neonates, laboratory workers, physicians, dentists, agriculturalists (for example, Rocky Mountain Spotted Fever; Q Fever; Lassa and Ebola Fevers; and *P. aeruginosa*, a particular problem for cystic fibrosis patients).

Phase 3. Review of diseases of importance to the less technologically advanced nations (for example, malaria, other parasitic diseases, and the bacterial diarrheas).

Major Issues or Problems Cited by Organizations Within the Administration, Congressional Committees and Organizations, and Interest Groups

None.

Major Barriers and Issues Relating to Program Performance

- If HHS decides to proceed with this Initiative as originally proposed, members of the Interagency Management Group should be appointed and resource issues resolved at an early date.
- Academic, industrial, and governmental cooperative research endeavors may be impeded by issues of research secrecy, proprietary rights, and competition for patent rights.
- Recruitment of volunteers for the clinical trials which are a necessary component part of vaccine development programs may be complicated because of unresolved compensation/liability issues.

- The growing inflexibility of budgetary allocations will place serious limitations on the Institute's ability to respond to breakthroughs with the timely initiation of new targeted research and development projects.

Documentation

(1) U.S. Department of Health and Human Services, "Health Research Activities of the Department of Health and Human Services," NIH Publication No. 81-2319, Public Health Service, National Institutes of Health, Bethesda, Md. 1980.

(2) U.S. Department of Health, Education, and Welfare, "Healthy People," DHEW (PHS) Publication No. 79-55071, Washington, D.C., U.S. Government Printing Office, 1979.

(3) U.S. Department of Health and Human Services, "Promoting Health Preventing Disease," DHHS (PHS) Washington, D.C., U.S. Government Printing Office, 1980.

(4) U.S. Department of Health, Education, and Welfare, "Virology, NIAID Task Force Report, Summary and Recommendations," DHEW Publication No. (NIH) 78-1836, Public Health Service, National Institutes of Health, Bethesda, Md. 1978.

(5) U.S. Department of Health and Human Services, "Sexually Transmitted Diseases, NIAID Study Group," NIH Publication No. 81-2213, Public Health Service, National Institutes of Health, Bethesda, Md. 1981.

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

Director's Overview

The central challenge today in biomedical research is control of chronic, disabling disease. As a result of medical progress, the population of the U.S. is living to be older, on the average, than ever before. This "graying of America" is expected to increase sharply the number of people at risk for chronic and disabling conditions.

Chronic diseases such as arthritis, diabetes mellitus, and digestive and kidney diseases cause disability, pain, and financial depletion and threaten premature death for millions of Americans. The burden of chronic diseases is one of America's most severe and fastest growing health problems.

The primary causes of most of these diseases remain largely unknown. Researchers have, however, implicated a number of factors, including heredity, abnormal immune system reactions and, in some cases, infectious agents, in the pathogenesis of these diseases. Building on research advances and dramatic improvements in research technology, investigators are pursuing many lines of productive research in the cause, diagnosis, and treatment of chronic disease. The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is leading this research nationwide on a wide range of diseases clustered into four groups:

- Arthritis, musculoskeletal, and skin diseases;

- Diabetes, endocrinology, and metabolic diseases;

- Digestive diseases and nutrition;

- Kidney, urologic, and blood diseases.

The Institute's highest priority is to foster fundamental and clinical investigator-initiated research on life processes in health and disease. This research is designed to improve the nation's ability to prevent, diagnose, and treat the wide variety of disease entities and conditions within the scope of the NIADDK mandate. Scientists in every discipline cooperate in this effort to understand the complex interplay of factors involved in the natural history and management of chronic disease. When scientific opportunities emerge, NIADDK also initiates applied and developmental studies to improve the effectiveness of medical care.

Another high Institute priority is research training. Against a background of a generally diminishing involvement of physicians in research, NIADDK supports a strong manpower development program noted for its emphasis on clinical research. NIADDK also sponsors effective activities for transferring new knowledge to the medical community and public. Through its programs, the Institute aims to alleviate human suffering and contribute to reducing the costs of medical care.

FY 1981

In all four areas of Institute programs, there have been major advances and newly-emerged areas of special research promise. A few selected accomplishments and opportunities are listed here.

Arthritis, Musculoskeletal, and Skin Diseases

- Treatment of scleroderma (systemic sclerosis) with the drug Captopril improves kidney function, lowers blood pressure, reduces ulcers on the fingers, and softens hardened skin in this grave, progressive condition.
- Effective treatment of rheumatoid vasculitis with agents affecting the immune system is stimulating new research on the role of immunity in the pathogenesis of rheumatic diseases.
- Long-term management of rheumatic conditions is enhanced by dramatic developments in biomaterials, surgical techniques, and function of joint and musculoskeletal prostheses.
- Successful bone marrow transplantation between siblings apparently halts progress of the rare but fatal bone disorder, infantile malignant osteopetrosis ("marble bone disease"), and excites new effort in transplantation techniques.
- A new effective treatment utilizing 13-cis retinoic acid has been developed for patients with severe, pustular, intractable acne--which previously almost invariably led to permanent disfigurement.

Diabetes, Endocrinology, and Metabolic Diseases

- Recombinant DNA research has laid the foundation for the production of artificial insulin. Industrial production of such insulin for routine use is now contemplated and the first clinical observations of the effectiveness and safety of this synethetic insulin have been initiated.
- Human growth hormone produced by recombinant DNA techniques is becoming available to supply the hormone previously obtained only by extraction from human pituitary glands at autopsy.
- Development of new tests may make possible more reliable identification of people who carry the defective gene for cystic fibrosis (CF)--the most lethal inborn error of metabolism among Caucasian children.

Digestive Diseases and Nutrition

- Improved endoscopic instrumentation has led to innovative research, diagnosis, and nonsurgical therapy of digestive diseases. Research on control of upper gastrointestinal bleeding with endoscopic systems--involving laser coagulation, electrocoagulation, suture clips, tissue glues, and thrombin and fibrinogen preparations--shows promising results.

- Monooctanoin, an emulsifying agent derived from digested fat, has been shown to be an excellent solvent for removal of gallstones and gravel retained in the common duct after gallbladder surgery.

- The principles of sonar have been applied to the diagnosis of digestive diseases. The echoes from sound waves are used to produce an image of the location, size, and contents of internal organs. With this method, ultrasonography, it is possible to make the diagnosis of gallstones and of cysts in the pancreas.

- Nutrition studies in the area of "total parenteral nutrition" (TPN) have resulted in development of an effective system for providing complete nutritional intake through solutions given by vein. This now provides for decreased morbidity and mortality in surgical patients in general and makes possible long-term continuation of life for patients who have lost the use of most of their intestinal tract through disease, trauma, or lifesaving corrective surgery. TPN is also a heretofore unavailable tool to study the human requirements for previously not recognized essential micronutrients.

Kidney, Urologic, and Blood Diseases

- Treatment with plasmapheresis and immunosuppressive drugs evidence dramatic reversal of kidney lesions in some patients with Goodpasture's syndrome, a severe disturbance of the immune system.

- A new investigative tool, isolated glomerular perfusion, makes possible for the first time well-defined determinations on immunologic pathogenesis of renal disease and the effects of pharmacologic agents on glomerular dynamics.

- Demonstration of prolonged cadaver graft survival with multiple pretransplantation blood transfusions produces recommendations for more liberal transfusions of dialysis patients slated for cadaver kidney transplants to ensure the longest possible graft effectiveness.

- Research results with Continuous Ambulatory Peritoneal Dialysis (CAPD), a new experimental treatment option for chronic renal failure, promise improved control of blood chemistries and fluid balance at lower cost than with conventional dialysis techniques.

- A safe and sensitive method has been developed for prenatal diagnosis of sickle cell disease, based on analysis of DNA from amniotic fluid cells that surround the fetus instead of, as formerly necessary, fetal blood. This method is also applicable to Cooley's anemia and may be applicable to a variety of genetic diseases.

FY 1982 Program Changes

Overall, NIADDK program changes in Fiscal Years 1982 and 1983 favor increased emphasis on traditional research project grants and research training opportunities. Modest increases should also be possible in Research Career Development Awards. A very restricted number of clinical trials are scheduled for initiation, most notably one on diabetes and its complications.

Examples of highest program priorities for FY 1982 and 1983 in each NIADDK funding area follow.

Arthritis, Musculoskeletal, and Skin Diseases

- Research on diseases distinguished by the important influence of genetic, immunologic, and possibly, infectious factors in their etiology: rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis.

- Basic and clinical studies in bone metabolism and disease and, in connection with osteoporosis, preventive/therapeutic approaches involving fluoride, calcium, and hormone supplementation.

- Studies on the pathogenesis of low back pain.

- Extension of a study of 1,300 patients treated with PUVA (ingested psoralens and high doses of long-wave ultraviolet) to determine whether there are long-term adverse effects of this treatment. Recent research results show that psoriatics previously treated with x-rays are at greater risk for squamous cell carcinoma following PUVA.

- Research on the role of proteolytic enzymes as therapeutic agents in epidermal diseases.

Diabetes, Endocrinology, and Metabolic Disease Program

- Initiation of the planning phase of a cooperative clinical trial on the relationship between the degree of blood glucose control and the long-term complications of insulin-dependent diabetes mellitus. The trial would compare the effect of customary diabetic management with an intensive therapeutic program designed to maintain near-normal blood sugar levels.

- Extension of studies in animals on transplantation of insulin-producing beta cells as an approach to the treatment of diabetes mellitus and its complications.

- Research on peptide hormones within the central nervous system, emphasizing their nature, cellular locus of receptors, and intrinsic mechanisms mediating their action.

- Research on enzymes in metabolic diseases, including isozymes and mutant enzymes in metabolic diseases and enzyme inhibitors and their role in treatment of metabolic diseases.

- Studies on organ-specific enzyme replacement therapy in metabolic diseases, particularly on intracellular uptake of active replacement enzymes.

Digestive Diseases and Nutrition

- Research involving the application of endoscopy to diagnosis and therapy of gastrointestinal disorders.

- Studies concerning the role of hormonal peptides found in the brain and gastrointestinal tract in regulation of secretion and motility of different segments on the digestive tract.

- Initiation of a multicenter, controlled clinical trial on endoscopic control of upper gastrointestinal bleeding as an alternative to surgery. Two modalities now used in clinical settings in conjunction with the fiber-optic flexible endoscope, electrocoagulation and electrocautery, will be tested for safety and efficacy.

- Clinical studies on the prevention of gastric and duodenal ulcers and upper gastrointestinal bleeding--to investigate the safety and efficacy of several newly developed agents purported to exert "cytoprotective" properties at the level of the mucosa of the upper gastrointestinal tract.

- Development of a system for differentiating between etiologically distinct types of obesity to aid research on the causes of obesity and to initiate rational individualization of therapy for this major public health problem.

- Research on bacterial adhesion to the intestinal mucosal surface and its relationship to the pathogenesis, prevention, and treatment of infectious diarrheas.

Kidney, Urologic, and Blood Diseases Program

- Immunologic studies related to chronic renal failure, including research on causative mechanisms, specific therapies to prevent progress to the end-stage renal diseases phase, and prevention of kidney transplant rejection with improved immunosuppressive therapy.

- Research on benign prostatic hyperplasia (BPH), emphasizing elucidation of etiologic factors.

- Improved understanding of the mechanisms by which cobalamin deficiency leads to anemia and other illness. The biochemical role of cobalamins (Vitamin B_{12}) in DNA synthesis and other essential cell processes is unclear. Deficiency may lead to disease, yet only two cobalamin-dependent enzymes are known, neither directly in the pathway of DNA synthesis. More information is needed on reactions of cobalamins in animal cells, the contribution of intestinal bacteria to cobalamin absorption and malabsorption, and the inconsistency of appearance of clinical signs of cobalamin deficiency-induced anemia in human populations.

FY 1983 Program Changes

Arthritis, Musculoskeletal, and Skin Diseases Program

- Research on the etiology and therapy of systemic connective tissue diseases: systemic lupus erythematosus, polymyositis, scleroderma, and polyarteritis nodosa.

- Multidisciplinary research to improve day-to-day function and long-term prognosis of artificial joints.

- Research on exercise pathophysiology, emphasizing the positive and negative influences of these activities and mechanisms of injury and repair.

- Investigation of the mechanism of action and of further applications of low-voltage current and electromagnetic stimulation for repair of bone injuries, a successful therapeutic technique for correcting non-union of fractures.

- Study of the formation of monoclonal antibodies to human epidermal structural proteins, the keratins, and to human epidermal cell membranes, using a new technique for developing such antibodies.

- Further evaluation of chemotherapeutic drugs--shown in a recent study to produce clinical improvement--for topical use in psoriasis.

Diabetes, Endocrinology, and Metabolic Diseases Program

- Studies on the cardiovascular, ocular, neurologic, and obstetric and perinatal complications of diabetes mellitus.

- Investigation of non-invasive and implantable metabolite sensors for use in diabetes research.

- Stimulation of studies on the behavioral and psychosocial aspects of diabetes mellitus.

- Research on use of recombinant DNA techniques to produce selected polypeptide hormones. Candidates include anterior pituitary hormones, such as prolactin, gonadotropic hormones, and TSH, as well as parathyroid hormone and human growth hormone and related factors.

- Re-orientation of priorities within the hormone distribution program to add new products and increase testing of products.

- Development of large, specialized spectrometers to make possible non-invasive studies of metabolic processes.

- Development of improved animal models to study diabetes mellitus and its complications and other inborn errors of metabolism.

Digestive Diseases and Nutrition

- Investigation of new methods to prevent cholesterol gallstone formation in individuals at high risk for the disease. The planned initiative will encourage multidisciplinary and epidemiologic research and may include a clinical trial of prophylactic therapy in a high risk population.

- Research on the pathogenesis, diagnosis, treatment, and prevention of pancreatic disease.

- Support of collaborative studies of pigment gallstone disease.

- Research on liver and pancreas transplantation, particularly rejection phenomena, alternate support systems, tissue regeneration, neurohumoral factors, and auxiliary transplantation.

- Planning of multicenter clinical trial to evaluate the efficacy of total parenteral nutrition (TRN), defined enteric formula diets (DFD), and other modes of nutritional support in patients with inflammatory bowel disease or short bowel syndrome.

Kidney, Urologic, and Blood Diseases

- Research on the causes of disorders leading to end-stage renal disease (ESRD) and the diverse pathogenetic mechanisms responsible for loss of kidney function. The program will encourage investigations on etiologic factors in ESRD, including nephrotoxins, genetic and developmental abnormalities, immune dysfunction, and diabetic nephropathy, as well as unsolved problems in therapy, such as organ preservation, allograft survival and complications of dialytic maintenance therapies. Advances in this area can have a significant impact on health care costs.

- Study of the production and action of erythropoietin. Recent developments in harvesting this hormone from large-scale culture systems are expected to result shortly in a complete analysis of the structure of erythropoietin, making possible its synthesis in theretofore unavailable quantity and purity. Past investigations, restricted because of the short supply of this substance, such as research involving the use of erythropoietin in anemia of chronic renal failure, would be given new impetus.

- Study of normal and abnormal red cell membrane structure and functions. Efforts will be encouraged to characterize the structure of the red cell membrane in normal and pathologic states, most notably hereditary spherocytosis, hemoglobinopathies, and oxidant-induced injury.

Potential Impact of Program Changes on Three-Year Period (1983-1985)

The greatest single impact of the program changes described in this year's plan should result from initiation of the planned clinical trial on diabetes. This cooperative trial will test the relationship between blood glucose control and the long-term clinical complications of insulin-dependent diabetes mellitus (IDDM). The trial would compare the effect of newly-developed intensive treatment programs capable of maintaining near-normal blood sugar levels with the results of customary management of IDDM. Pilot trials are scheduled for fiscal years 1983 and 1984. Given evidence of feasibility in these pilot trials, initiation of the full-scale trial should occur in fiscal year 1985. This trial will be funded by a cooperative agreement.

Also likely to have a significant impact is the planned initiation of a multicenter, control clinical trial on endoscopic control of upper gastrointestinal bleeding. Two modalities now used in clinical settings in conjunction with the fiber-optic flexible endoscope, electrocoagulation and electrocautery, will be tested for safety and efficacy. These procedures, if proven safe and effective, will provide an urgently needed alternative to surgery--with its high operative mortality, morbidity, and cost. This trial is now scheduled to begin in FY 1983 and continue through FY 1985.

NIADDK

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

DATE: FEB 23 1981

TO : Director
National Institute of Arthritis, Metabolism
and Digestive Diseases

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It is especially gratifying to note the significant research accomplishments that have been achieved in many of the health areas within the purview of the NIAMDD. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

NIADDK administers research and training programs covering a wide range of diverse categorical disease areas. The goal of the NIADDK is to maintain a balanced program of basic and clinical research in illnesses characterized by chronicity and long-term disability. The breadth of responsibilities of the NIADDK is reflected in the continuing interest of a large number of diverse constituency groups and voluntary organizations and in the Congressional mandates for specific program elements within the Institute.

Impact of Stabilization

- In 1981 the number of competing research project grants was nearly equal to the 1979 level, after a decline in 1980. A substantial increase in the number of grants is planned for 1982.

- Because research project grants have historically received over 60 percent of the funding of NIADDK, proportionately small amounts made available for grant (R01) stabilization from other support mechanisms reduce the total funds for other nongrant areas (centers, contracts, intramural) significantly.

- Under the stabilization initiative, no new Research Career Development Awards will be funded in 1981. In 1982 and 1983, NIADDK plans to expand career awards over the 1980 total.

- Training awards decreased substantially from the 1980 level in 1981 and further decreases are planned in 1982.

- Intramural research funds and manpower are projected to remain constant during the 1980-83 period.

- NIADDK's existing obligations to research centers cannot be honored with funds available in the President's Budget for 1981. Cost of living increases will be planned in 1982, with some program growth in 1983.

Research Advances and Opportunities

- A life-saving drug treatment (Captopril) for scleroderma patients has been developed, which improves kidney function, lowers blood pressure, reduces digital ulcers, and softens hardened skin.

- Successful treatment of rheumatoid vasculitis with an immunosuppressive drug has stimulated research on circulating immune complexes in rheumatic disease.

- A cooperative clinical trial on the relationship between blood glucose control and vascular complications of insulin-dependent diabetes mellitus is planned. The study will be implemented in discrete phases, with the built-in ability to discontinue the study at given points if it is found that the study requirements exceed present techniques. Following research design and feasibility studies, the conduct of the study would require at the least five to seven years before any demonstrable difference between the experimental and control groups could be measured.

- Basic research using recombinant DNA techniques has laid the foundation for human growth hormone and insulin production *in vitro*.

- Improved endoscopic instrumentation and techniques have led to innovative research and better diagnosis and therapy of digestive diseases.

- An emulsifying agent derived from digested fat (monooctanoin) has been shown to dissolve gallstones remaining in the common duct after gallbladder surgery.

- Evidence that treatment with plasmapheresis and immunosuppresive drugs can cause dramatic reversal of kidney lesions in some patients with Goodpasture's syndrome (a severe disturbance of the immune system) has encouraged further research on the effect of such treatment on kidney disease.

- Recent research has demonstrated that the success of cadaver kidney transplants increases with the number of pre-operation blood transfusions.

- Research results with Continuous Ambulatory Peritoneal Dialysis, an experimental treatment for chronic renal failure, promise improved blood chemistry and fluid balance at a lower cost.

Health Programs Extension Act of 1980

- P.L. 96-538, the Health Programs Extension Act of 1980, requires the submission of a memorandum of reorganization. An "implementation package" is in preparation. The previously existing (but now expired) Diabetes Advisory Board is to be organizationally moved from the Office of the Director, NIH, to NIADDK, and a new advisory board for digestive diseases has been created. The expired Arthritis Advisory Board (previously attached to NIADDK) has been recreated by the Act. The screening process for members has begun; however, additional personnel will be required to staff all three Advisory Boards created by this Act.

  NIADDK sees in P.L. 96-538 a reflection of the Congressional and Departmental desire to extend to the Institute's four major programs--

Arthritis, Diabetes, Digestive Diseases, and Kidney Diseases--the visibility and importance which their large outside constituencies have increasingly demanded from the Congress and Executive Branch, which could be done by elevating the Institute to Bureau status. Such status for the newly Congressionally-reorganized NIADDK would be highly desirable administratively and would not require additional funds, positions, or facilities.

NIADDK

Health Programs Extension Act

Statement of Issue

Implementation of the Health Programs Extension Act of 1980.

Discussion of Issue

NIADDK is distinctive in bearing the most diverse categorical disease responsibilities of all the institutes at NIH. Research supported by the Institute impacts upon the Nation's most important chronic and disabling diseases. For some time, NIADDK has been called upon to exert significant leadership both within NIH and with other agencies regarding the diseases within its purview. A series of legislative actions, culminating in the Health Programs Extension Act of 1980 (P.L. 96-538) has combined to enhance the prominence and authority as well as to increase the responsibilities of the Institute's national programs. While NIADDK has reorganized unofficially to meet these foreseen official responsibilities, neither its personnel power nor its standing within the NIH community has evolved to the degree commensurate with these Congressional directives.

P.L. 96-538 reflects the Congressional and Departmental desire to extend to the Institute's four major programs--Arthritis, Diabetes, Digestive Diseases, and Kidney Diseases--the visibility and importance which their large outside constituencies have increasingly demanded from the Congress and Executive Branch. This legislative action parallels to a large degree the 1971 and 1972 reorganizations by Congressional mandate of two other Institutes of the NIH: the National Cancer Institute and the National Heart, Lung, and Blood Institute. As a result of these reorganizations, these institutes became bureaus--a fact which facilitated considerably their subsequent activities because of the delegations of authority and other administrative advantages connected with Bureau status. Bureau status for the newly Congressionally-reorganized NIADDK is highly desirable administratively for similar reasons, but does not require additional funds, positions, or facilities. Moreover, Bureau status would enable the Institute to designate its four major program clusters--(1) Arthritis, Musculoskeletal, and Skin Diseases, (2) Diabetes, Endocrine, and Metabolic Diseases, (3) Digestive Diseases and Nutrition, and (4) Kidney, Urologic, and Blood Diseases--as Divisions to give them the necessary and politically desirable visibility which they lack currently.

PROGRAM PERFORMANCE SUMMARY

DIABETES PROGRAM

Program Description

Diabetes mellitus is a major public health problem in the United States today. Recent awareness of this fact has brought increased support to the National Institutes of Health for diabetes research as well as to other HHS agencies to develop new health care, control, and education programs. Federally supported diabetes activities transect the organizational boundaries of many individual agencies, Institutes, and Programs. However, the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) has the lead responsibility for implementing and coordinating the national effort to combat diabetes, especially with respect to research programs. There is active coordination with other NIH Institutes and HHS agencies involved in additional diabetes-related research or community activities.

Scope

Diabetes affects an estimated 10 million Americans. It is the fifth leading cause of death by disease in the United States, accounting for approximately 40,000 deaths per year among those known to have the disease. If the complications resulting from diabetes--heart disease, kidney disease, blindness, gangrene, and damage to the nervous system, among others--are included in the figures, the death rate is third only to cardiovascular disease and cancer. The economic impact on this Nation through mortality, disability, direct medical expenses, drug costs, and lost time from work is estimated to be approximately $7 billion annually.

Clearly the personal, social, economic, and public health problems of diabetes are enormous. Moreover, the prevalence of the disease appears to be increasing approximately 6 percent annually. Although great progress is being made through NIH-supported research, the present state of knowledge remains insufficient to prevent or cure diabetes, or even to provide patients with optimally effective treatment.

Collectively, the NIH Diabetes Program and related activities supported by the other agencies represent approximately a $150 million Federal effort (approximately $145 million for NIH in FY 1981). As detailed below in Program Objectives and Activities, the primary administrative focus of this effort is in the approximately $75 million NIADDK Diabetes Program, with its major emphasis on investigator-initiated basic and clinical studies related to the etiology, epidemiology, and pathogenesis of diabetes. Associated with this fundamental research effort are programs involving resource, technology, and manpower development, clinical applications, training, data analysis, and information dissemination which complement the diabetes research, control, education, and health care services activities supported by other agencies.

Legislative History

In July 1974, the National Diabetes Research and Education Act (P.L. 93-354) established a National Commission on Diabetes to assess existing needs and opportunities and to formulate a long-range plan for future activities. This Act also authorized the establishment of multipurpose Diabetes Research and Training Centers and mandated establishment of an interagency Diabetes Mellitus Coordinating Committee. Following an extensive series of public hearings, the National Commission on Diabetes submitted reports to Congress in December 1975 and November 1976. These reports recommended a series of specific long-range programs for expanding and coordinating the national research effort in diabetes and for accelerating the development of programs in diabetes health care, control, and education. The Commission also recommended the establishment of a National Diabetes Advisory Board, which the Congress authorized in September 1976 (P.L. 94-562).

Based on the Commission's recommendations, the Congress appropriated additional funds to NIH in FY 1977 to implement the recommendations for diabetes research. Most of these new funds were earmarked and appropriated to the NIADDK, the Institute with lead responsibility for diabetes research. Since 1977 the Appropriations Committees of the Congress have continued to express a clear and strong interest in diabetes research, and the program continued to expand significantly through 1980.

In December 1980, Public Law 96-538 changed the Institute name to include "Diabetes"--National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. It extended authorization for the Diabetes Research and Training Centers and reauthorized establishment of a National Diabetes Advisory Board and a Diabetes Mellitus Interagency Coordinating Committee. In addition, this legislation provided a statutory basis for the NIADDK's National Diabetes Data Group and National Diabetes Information Clearinghouse, both of which had been established by the Institute in accordance with recommendations of the National Commission. Furthermore this legislation also provided a statutory basis for the NIADDK's Associate Director for Diabetes, Endocrinology, and Metabolic Disease (DEMD), and for various trans-NIH responsibilities which previously had been delegated to this position by the Director, NIH. It also provided for subcommittees for arthritis, diabetes, and digestive diseases in the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council.

Program Resources

- Fiscal Resources. Table 1 (below) summarizes the NIADDK program budget in diabetes for Fiscal Years 1978-1982.

- Personnel Resources. At the present time, a total of approximately 100 full-time-equivalent permanent staff positions are directly affiliated with the NIADDK's diabetes programs (86 intramural and 14 extramural). In addition, however, many NIADDK staff associated with centralized functions also contribute directly and indirectly to supporting the Institute's various diabetes-related initiatives. The estimated prorated share of NIADDK staff positions attributable to the Institute's diabetes activities based on funding level is approximately 120.

Table 1

Diabetes Program Budget for Fiscal Years 1978-82(1)
(Dollars in Thousands)

	1978	1979	1980	1981(2)	1982(3)
Research Grants	$33,076	$38,912	$40,686	$46,605	$46,957
Center Grants	9,663	9,046	10,219	10,137	11,637
Career Awards	1,826	2,032	2,485	2,116	2,769
Training (NRSA)	3,391	3,380	5,086	4,710	3,464
Contracts	1,213	3,487	4,385	2,210	4,860
Extramural subtotal	$49,169	$56,857	$62,861	$65,778	$69,687
Intramural Research	3,804	4,214	5,741	6,457	6,852
Program subtotal	$52,973	$61,071	$68,602	$72,235	$76,539
Program total(4)	$55,208	$63,492	$71,329	$75,049	$79,475

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(1) Excludes "diabetes-related" research grants in nondiabetes programs (OX-OX-03).

(2) Current estimate.

(3) Reagan budget (March 1981).

(4) Includes administrative costs.

Program Objectives and Activities

Program and Management Objectives

- To expand basic and clinical research efforts on diabetes mellitus and its complications in order to capitalize on recent research advances and identified needs.
- To expand the application of research knowledge through prototype development and clinical trials.
- To train an adequate number of research workers in order to provide a source for future investigators.
- To foster the transfer of information generated in the research laboratory to the health care system.
- To coordinate efforts concerning diabetes mellitus within the NIH and across the Federal Government.

Program Activities

Diabetes Research. The NIADDK supports a wide variety of diabetes and diabetes-related projects ranging from basic and clinical biomedical research to epidemiological and behavioral investigations through the investigator-initiated research grants program, project grants, new investigator research awards, and research and development contracts (see Table 1). This support spans the range of scientific disciplines which are related to diabetes mellitus and its complications. Diabetes related research grants in the Institute's nondiabetes programs (kidney, hematology, endocrinology, and the like) are supported with Diabetes Program funds, which amounted to approximately $12.5 million in FY 1980. The Diabetes Program also supports a Centers Program (Obesity Center) in another of NIADDK's programs.

Diabetes Centers. The Diabetes Centers Program administers two types of centers awards which foster interdisciplinary cooperation among groups of established investigators: the Diabetes-Endocrinology Research Centers program (DERC) and the Diabetes Research and Training Centers program (DRTC). The DERCs are exclusively oriented toward biomedical research, while the DRTCs include training and information transfer components as well. For both types of centers, the grants provide for core facilities (shared resources), pilot and feasibility studies (new initiatives), and limited funds for program enrichment.

Diabetes Manpower/Resources. The Institute supports research training and career development and research resources related to diabetes through the DEMD Resources and Manpower Development Program. Table 1 illustrates the respective levels of support for fiscal years 1978 through 1981.

National Diabetes Data Group. The National Diabetes Data Group consists of a nationwide group of expert advisors including epidemiologists, individuals with expertise in the research, nutritional, and socioeconomic aspects of diabetes, and representatives from Federal agencies and voluntary organizations. The National Diabetes Data Group collects, analyzes, and disseminates data on diabetes and its complications.

Diabetes Clearinghouse. The National Diabetes Information Clearinghouse has three major goals: to increase the availability of accurate diabetes information for health care professionals, for patients, and for their families; to increase community awareness and understanding of diabetes as a major health problem; and to establish a viable system for speedy communications about new developments, techniques, and programs in diabetes among all sections of the diabetes community. In discharging its responsibility, the Clearinghouse collects and disseminates information about educational materials, programs, and resources, and is establishing criteria and a mechanism for evaluating nonscientific printed diabetes education materials.

Diabetes Program Liaison/Coordination. In accordance with NIADDK's lead role in coordinating the Federal diabetes effort, the staff of the DEMD Diabetes Program Branch has been involved extensively in liaison with other diabetes-related programs in both the public (Centers for Disease Control, Indian Health Project, National Center for Health Statistics, etc.,) and private (American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators, etc.) sectors.

In addition, close coordination of diabetes-related initiatives in other NIH Institutes has been achieved through active staff support of the Trans-NIH Diabetes Coordinating Committee, in other Federal agencies through the interagency Diabetes Mellitus Coordinating Committee, and with the overall national diabetes program through close liaison with the National Diabetes Advisory Board and staff support of its various activities.

Evidence of Program Performance

Type of Evidence

Review. All research grant applications and contract proposals assigned to the Diabetes Program are regularly reviewed for scientific and technical merit through the NIH peer review system. The rigorous scrutiny of the NIH peer review system, through its periodic evaluation of all grant applications and contract proposals, is fundamental to maintaining the high quality of the Institute's Diabetes Programs.

The Diabetes Programs are also periodically reviewed by senior NIH/NIADDK staff. The Director, NIH, conducts a formal annual review of diabetes-related activities with the Associate Director, DEMD, and members of the NIH Diabetes Coordinating Committee. In addition, the Director, NIADDK, reviews competing research grant applications with staff prior to each of the Institute's three annual National Advisory Council meetings, and also conducts a comprehensive program review in conjunction with development of the Institute's annual research plan. Furthermore, the Associate Director, DEMD, meets weekly with program staff, and through this process each program component and initiative is scrutinized and reviewed on a continuing basis.

Monitoring. Each program component and initiative is continually reviewed and assessed by DEMD staff in order to evaluate progress and identify emerging needs and opportunities. Program staff also review annual progress reports submitted for noncompeting applications and conduct on-site visits at selected grantee laboratories.

Evaluation. During FY 1980, program staff developed a conceptual framework and initiated an expanded data collection and analysis effort to facilitate the Department's Congressionally mandated annual evaluation of the Diabetes Research and Training Centers.

In cooperation with the Department, an evaluability assessment of the National Diabetes Information Clearinghouse is being implemented.

There exists a statutory mandate for annual evaluation of the activities of the Diabetes Research and Training Centers, results of such evaluations to be reported to the Congress annually. A contractor has been selected during FY 1980 to identify or to develop methodologies for a formal independent evaluation of NIADDK centers programs, including both the Diabetes Research and Training Centers and the Diabetes Endocrinology Research Centers.

Various aspects of the Diabetes program are evaluated by the DEMD Subcouncil. In addition to its role in the review of grant applications, the Subcouncil informally evaluates other components of the program. During FY 1980, these additional activities included a review of the National Diabetes Data Group. Furthermore, the Subcouncil also serves in a prospective role as a "sounding board" in evaluating plans for future program activities. In this regard, the Subcouncil has recently evaluated plans related to both the program's automated insulin delivery systems contracts and the proposed clinical trial to assess the relationship between metabolic control and the complications of diabetes.

Several audits have been made of all federally-supported diabetes activities by the General Accounting Office (GAO). The GAO has been interested in ascertaining the extent to which various agencies have been able to address the goals of the Long-Range Plan To Combat Diabetes. A final report from the primary audit has recently appeared.(7)

In accordance with a statutory mandate, progress in the field of diabetes has been evaluated periodically by the National Diabetes Advisory Board (NDAB), and its findings and recommendations have been reported annually to the Congress and the Secretary, HHS.(2,3,4)

The DEMD relies on a Director's Advisory group and other ad hoc advisory groups to assess the status of DEMD program plans and initiatives.

Evidence of Effectiveness Related Directly to Stated Program Objectives

To Expand the Base of Basic and Clinical Research. Support for research grants has increased modestly since 1978. The program has stimulated an interest in diabetes and its complications by issuing the following program announcements: broad multi-institute program announcement on diabetes and its complications; epidemiology; behavioral research; and the kidney. Furthermore, it has held an average of two to three workshops annually on such topics as immunology, automated insulin delivery systems, the etiology and pathogenesis of diabetes, and on animal models of diabetes.

Attachment A (at the end of this section) illustrates a few of the numerous research advances made during the period 1978-81.

To Expand the Application of Research Knowledge. Five years of planning have culminated in an RFA for clinical centers and an RFP for a coordinating center to participate in the planning and feasibility testing of a multicenter, randomized clinical trial to assess the relationship between metabolic control and the prevention/arrest/remission of the microvascular complications of insulin-dependent diabetes. The trial will begin in late 1981.

A program of research and development on automated insulin delivery systems has been initiated and is drawing to a successful conclusion. After an assessment of this contract program, the Diabetes Program has concluded that the state of the art has been adequately developed so that future NIADDK support for studies in this area should be available to the scientific community through investigator-initiated research grants.

The role of the DRTCs in the transfer of knowledge is effected through their training and information transfer component and directed toward health professionals. Since there are only a limited number of DRTCs, this challenge is being met through the centers' development of new and innovative programs (such as curriculum manuals and development of and education in the team concept) for training and continuing education for health professionals. Once these programs are developed, tested, and evaluated at the center and within the local area, they are usually available for wide distribution. Centers are encouraged to deposit their materials with the National Diabetes Information Clearinghouse, to ensure that availability of the programs is widely known.

To Maintain an Adequate Level of Support for Training. As the report of the Diabetes Research Manpower and Training Subcommittee of the Trans-NIH Diabetes Coordinating Committee indicates,(6) support for both research training and research career development in diabetes and related areas increased sharply from 1976 through 1978, with funding continuing at a more moderate rate since 1978.

To stimulate interest in diabetes and related research training and career development, the NIH Diabetes Program has initiated two new awards: the Special Emphasis Research Career Award for clinician-researchers; and the New Investigator Research Award, which functions much as a "junior" grant by providing researchers who have not yet held a grant an enhanced opportunity to obtain research support of their own.

To Foster Transfer of Information. The National Diabetes Information Clearinghouse publishes 8 to 10 bibliographies annually and a newsletter quarterly. A recent survey of newsletter recipients indicated a high degree of satisfaction with the newsletter and other Clearinghouse products.

A recent survey of Diabetes Centers provided a status report of training and information transfer activities. Centers have exported educational products, sponsored continuing education courses for a range of health care professionals, and established liaison with local voluntary or State agencies about diabetes-related information.

The National Diabetes Data Group has been responsible for the adoption internationally of a Classification System for Diabetes Mellitus and for the analyses of diabetes-related data from various national health surveys.

To Coordinate Diabetes-Related Efforts Within the NIH and Across the Federal Government. The Diabetes Mellitus Coordinating Committee (DMCC) publishes annually a compendium of Federal activities related to diabetes mellitus. Most recently it has initiated a project to distribute a primer detailing standards of health care for patients with diabetes through appropriate Federal agencies. The DMCC was also responsible for identifying an error in the projections of insulin supplies made by an FDA study, bringing this to the attention of the National Diabetes Advisory Board and the FDA, and as a result preventing widespread public alarm.

The trans-NIH Diabetes Coordinating Committee has continued to be responsive to its mandate and to be productive through the initiation of a number of different activities in FY 1980. It has fostered collaboration across Institutes resulting in the issuance of multidisciplinary program announcements and Special Emphasis Research Career Awards; sponsored a conference exploring the utility and promise of animal models of diabetes; prepared a computerized trans-NIH diabetes-related research data base; and recently reviewed and analyzed its current state of diabetes research and made specific recommendations for future opportunities and program initiatives in the areas of (1) etiology, pathogenesis, and epidemiology; (2) complications; (3) medical applications of research; and (4) research training and career development. A report to the Director, NIH, the Directors of all NIH Institutes, and the National Diabetes Advisory Board is being prepared.(6)

Other Evidence of Program Effectiveness

Attachments B and C (at the end of this section) display the outlays at NIH and across the Federal Government for diabetes and related research according to the categories developed by the Diabetes Mellitus Coordinating Committee. Other useful documents include the 1979 and 1981 reports to the

Director, NIH, from the Diabetes Coordinating Committee.(5,6) In addition, several reports of the National Diabetes Advisory Board(2,3,4) and of the GAO survey of the NIH Diabetes Program(7) are pertinent.

Studies of Effectiveness Now Under Way

- Centers Methodology Contract: a contract has been initiated to conduct an evaluability assessment of the NIADDK Centers Program, which includes the Diabetes Centers Program.
- Data collection activities are under way to examine training and information transfer activities, core facilities, and interdisciplinary collaboration at Diabetes Centers. In addition, archival information is being reviewed to examine changes in the breadth of the research base over time.
- An evaluability assessment of the National Diabetes Information Clearinghouse is now under way.

Proposed Studies To Assess Program Performance

DEMD has applied for evaluation set-aside funds to conduct an evaluation of the postdoctoral research training in diabetes, endocrine disorders, and metabolic diseases and an evaluation of products disseminated by the National Diabetes Information Clearinghouse.

Issues

The Ability of the NIADDK To Maintain the Diabetes Initiative

The remarkable scientific and programmatic accomplishments of the past five years have greatly increased the momentum in diabetes research, resulting in unprecedented opportunities and great promise for the future. Current growth, however, is consistent with a diminished availability of resources, which does not bode well for the future level of activity.

The Ability of the NIADDK To Support the Diabetes Clinical Trial

This trial will address the most critical issue in clinical diabetes today: whether control of blood glucose concentration to physiologic levels will prevent and/or ameliorate the complications of diabetes mellitus. The trial has been initiated after prolonged and thorough discussion throughout the scientific community and within the NIH resulting in a strong consensus that such a study should be undertaken immediately. The study, to be supported through the cooperative agreement research grant mechanism, is expected to require 10 years to complete, at a cost of approximately $2 million annually for the first 2 years and roughly $7 annually during the last 7 to 8 years.

The study began with the announcement of a Request for Application (RFA) in January 1981. Over 60 applications have recently been reviewed through the NIH Peer Review System. Participating clinics and a Coordinating Center are expected to be selected by the NIADDK National Advisory Council in October 1981 and the trial will begin shortly thereafter. Current NIADDK budget estimates for fiscal years 1982 and 1983, the first two years of the trial, indicate that support for the study would have to come from research grant funds, jeopardizing the Institute's ability to support its research grant program at the current level. The Institute's ability to support this important clinical trial depends completely on future availability of resources.

NIADDK Research Training and Manpower Development Programs

A continuous input of well-trained young scientists is indispensable to maintaining and expanding the current high level of research productivity and to capitalizing upon the many existing research opportunities that hold such great promise for improved treatment of diabetes and the eventual prevention and cure of this disease. The NIH is the principal source of support for research training in diabetes through a variety of programs at different levels within the continuum of research training and career development. During the past few years existing NIH programs for research training and career development have been greatly expanded and new concepts and programs have been introduced to provide increased and more varied opportunities for training in diabetes research. To a very large extent, maintenance of the current momentum in diabetes research and future success in the overall effort against diabetes are tied to the continued availability of a cadre of scientists trained in research through NIH-supported programs. This, in turn, depends on the continued availability of resources for the necessary training activities.

NIADDK's Role in Diabetes Information Transfer

One of the charges from the Director, NIH, to the Trans-NIH Diabetes Program was to serve through the National Diabetes Information Clearinghouse as the central resource for providing diabetes-related information and educational materials to scientists, health professionals, diabetics and their families, and the general public. The recently enacted Public Law 96-538 assigns responsibility for communication and education programs to NIADDK. The need for greater attention to education and information transfer was underscored by experts who attended a recent Health Care Delivery Conference sponsored by the National Diabetes Advisory Board (NDAB). The NDAB has recommended that the Centers for Disease Control take the lead responsibility in this area. While all agree that more attention be devoted to education and information transfer activities, the question remains as to where this function should reside and how much support it should receive.

Currently, the NIADDK's National Diabetes Information Clearinghouse (NDIC) is effectively discharging the information functions assigned to it. It has received many favorable comments from the diabetes community, as well as others, and has reflected well upon the NIADDK and the NIH. However, the Institute's ability to develop and foster new education and information programs identified by it and by the diabetes community, is governed by future availability of resources for this purpose. The proposed activities are an important component of the effort on diabetes.

Documentation

1. Diabetes Mellitus Coordinating Committee Sixth Annual Report to the Director, Fiscal Year 1978; NIH Publication No. 80-2243, 1980.
2. Third Annual Report to the National Diabetes Advisory Board--Five Years of Progress; Five Years of Promise, NIH Publication No. 80-2072, April 1980.
3. Report of the National Conference on Diabetes: Current Status and Future Directions, NIH Publication No. 80-2073, April 1980.
4. The Treatment and Control of Diabetes: A National Plan to Reduce Mortality and Morbidity, NIH Publication No. 81-2284, November 1980.
5. Report of the National Institutes of Health Diabetes Mellitus Coordinating Committee to the Director, National Institutes of Health, on Progress Towards Implementation of the Recommendations of the National Commission on Diabetes and the National Diabetes Advisory Board, 1979.
6. Report of the Trans-NIH Diabetes Coordinating Committee: Current Status and Future Directions, August 1981.
7. Federal Diabetes Activities, United States General Accounting Office, 1980.

Attachment A

Examples of Recent Research Advances in Diabetes

The following are just a few examples of the numerous research advances developed during the recent three-year period by Institute grantees or intramural research workers.

- Development of portable, automated, programmable insulin infusion pumps which permit experimental regulation and control of blood sugar levels in diabetic patients to a level not possible heretofore.
- Demonstration that use of these devices can improve motor nerve conduction in certain diabetic patients after several weeks of therapy.
- Elaboration of further evidence concerning possible viral causation of diabetes.
- Demonstration of a new type of diabetes due to the secretion of an abnormal insulin molecule.
- Demonstration that a high-plant-fiber, high-carbohydrate diet can reduce insulin requirements in type II diabetes.
- Demonstration that physical exercise and training can increase body tissue sensitivity to insulin and improves control of type II diabetes.
- Successful transplantation of insulin-producing pancreatic cells across species lines without the conventional short-term transplant rejection.
- Basic research using recombinant DNA techniques has laid the foundation for the subsequent industrial production of manmade insulin from genetically engineered bacteria.
- Development of new blood tests which reflect the overall (not momentary) level of blood sugar control in any given patient.
- Perinatal deaths have been cut in half in recent years through the use of improved methods for controlling blood sugar levels.

Attachment B

NIADDK

Total Federal diabetes-related activities by diabetes subtopics: FY 1979

Diabetes Subtopic	Funds
A. Epidemiology (see B 21)	
B. Research	
1. Resources	$ 2,369,451
2. Etiologic Factors including genetic, immunologic, infectious, and other factors relating to the cause of diabetes	5,566,665
3. Nutrition, Exercise, and Obesity	8,454,359
4. Hormones	19,330,805
5. Intermediary Carbohydrate and Protein Metabolism	11,934,133
6. Transplantation and Artificial Devices	4,688,831
7. Nonhormonal Blood Factors, Platelets, and Coagulation	1,582,179
8. Lipid Metabolism, Lipoproteins, Cholesterol, and Triglycerides	10,624,521
9. Pancreas and Islet Cell Studies	370,081
10. Microangiopathy	2,278,834
11. Macroangiopathy	1,324,148
12. Heart and Circulation	3,862,747
13. Central and Peripheral Nervous System	3,346,661
14. Nephropathy	1,635,040
15. Ocular Complications	15,482,911
16. Dental Complications	658,252
17. Infections	1,178,171
18. Pregnancy and Perinatal Problems	4,254,662
19. Psychosocial and Behavioral Problems	1,346,194
20. Pharmacologic Agents	1,910,733
21. Epidemiology	3,405,269
22. Health Services	3,000*
Subtotal - Research	$105,607,647
C. Health Care Delivery	
1. Health Care Facilities and Research	
2. Health Care Services	439,529
3. Social Adjustment and Mental Health Services	
4. Public Education	1,157,928
5. Patient Education	439,529
6. Quality Assurance	440,529
7. Health Care Financing	440,529
8. Health Planning and Evaluation	440,529
Subtotal - Health Care Delivery	$ 3,358,573
D. Manpower Development and Professional Education	
1. General	
2. Career Awards	2,492,325
3. Fellowships and Training Programs	4,508,028
Subtotal - Manpower Development and Professional Education	$ 7,000,353
E. Multidisciplinary Programs	$ 12,020,997
F. Workshops, Conferences, and Publications	$ 175,125
G. Unclassified	$ 298,124
TOTAL**	$128,460,819

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* *Funding amounts for CDC, NCHS, and VA were not provided for inclusion.*

** *Includes some diabetes-related intramural funds.*

FY 1979 diabetes-related funding by subject area and agency ($ thousands)[a]

	ADAMHA	CDC[b]	DRR	FDA	HRA	NCHS	NEI	NHLBI	NIA	NIAID	NIAMDD	NICHD	NIDR	NIEHS	NIGMS	NINCDS	USDA	VA
A. Epidemiology (see B 21)																		
B. Research																		
1 Resources			403					72			1,734				81	79	X	X
2 Etiologic Factors including genetic, immunologic, infectious, and other factors relating to the cause of diabetes			369				270	14		1,293	2,631	368	420	100	101		X	X
3 Nutrition, Exercise, and Obesity			2,281						159		3,873	1,190	90			201	660	X
4 Hormones	274		1,781	18				440	852	215	15,590	78			82		X	X
5 Intermediary Carbohydrate and Protein Metabolism			274						109		8,809	815			509	1,219	199	X
6 Transplantation and Artificial Devices			114					83		18	4,262	43			168			X
7 Nonhormonal Blood Factors, Platelets, and Coagulation			40					1,191			351							
8 Lipid Metabolism, Lipoproteins, Cholesterol, and Triglycerides			417					3,776	158		6,043	53			164	13		X
9 Pancreas and Islet Cell Studies									50	22	298							
10 Microangiopathy			65				104	1,375			582		110			42		X
11 Macroangiopathy			16					909	140							259		X
12 Heart and Circulation			64					3,671			101				26			X
13 Central and Peripheral Nervous System			111					172			902		70			2,091		X
14 Nephropathy			126					121		126	1,262							X
15 Ocular Complications			18				15,235	229										X
16 Dental Complications			13										645					X
17 Infections			72							1,009	97							X
18 Pregnancy and Perinatal Problems			605					385			632	2,632					X	
19 Psychosocial and Behavioral Problems	190		196					411			549							X
20 Pharmacologic Agents	X		1,008					21			794				87			X
21 Epidemiology		X				X	468	1,324			1,538				75		X	X
22 Health Services		X	3			X												X
Subtotal	464		7,976	18			16,077	14,194	1,468	2,683	50,048	5,179	1,335	100	1,293	3,904	859	
C. Health Care Delivery																		
1 Health Care Facilities and Research																		
2 Health Care Services		440				X												
3 Social Adjustment and Mental Health Services																		
4 Public Education		441	378															
5 Patient Education		440									339							
6 Quality Assurance		441																
7 Health Care Financing		441				X												
8 Health Planning and Evaluation		441																
Subtotal		2,644	378								339							
D. Manpower Development and Professional Education																		
1 General																		
2 Career Awards							157	241		41	2,053							
3 Fellowship and Training Programs	36				354		74	67		12	3,952	13						
Subtotal	36				354		231	308		53	6,005	13						
E. Multidisciplinary Programs											9,143	2,615				264		
F. Workshops, Conferences, and Publications											175							
G. Unclassified											200				94			
TOTAL FY 1979 FUNDING[c]	500	2,644	8,354	18	354	X	16,308	14,502	1,468	2,736	65,910	7,807	1,335	100	1,387	4,168	859	X

[a] Entries are inexact due to rounding of individual project amounts. X indicates activity reported but no funding data provided.

[b] CDC diabetes control demonstration projects cross-cut reporting categories B 21 22, C 2, and C 4 8.

[c] May include some diabetes-related intramural funds.

NATIONAL CANCER INSTITUTE

Director's Overview

Significance of the Health Problem

Cancer, the second most common cause of death in the United States, is the most dreaded of all diseases. Next year, over 40,000 Americans will die from cancer--accounting for one-fifth of all deaths--and about twice as many new cases (excluding nonmelanotic skin cancers) will be diagnosed. The impact of cancer is multifaceted. Cancer patients who are part of the workforce lose substantial amounts of income because of work-loss and the costs of treatment and care, which continue to rise. The physical and emotional pain experienced by the patient, his family, and friends must also be taken into account.

Although cancer is most frequently observed in senior citizens (in recent years between 50 and 55 percent of new cases occurred in those over 65), the patient dying from cancer still loses on the average over 15 years of life. Cancer occurs on the average somewhat earlier in life for women than for men. Less frequent in occurrence but significant, nonetheless, are the numerous children and youths who are diagnosed each year with cancer.

Trends in both cancer incidence and cancer mortality are affected by many factors. The overall incidence of cancer increased about one to two percent per year in the 1970s. The increase varies, however, from site to site, and a few sites (stomach, uterine cervix, total leukemia) actually decreased in incidence, the only major increase being in the incidence of lung cancer.

Trends in cancer mortality differ for different ages. Mortality has been increasing at about 0.5 percent per year for women and 1 to 2 percent for men. Men continue to have a higher incidence of the more lethal cancers such as stomach, pancreas, and lung. The age-specific mortality trends show declines for the young, relative stability for the middle aged, and increases for older patients.

The forms of cancer that make up the bulk of new cases in children and young adults are acute lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, and cancers of the brain, kidney, and bone. With recent improvements in treatment, increased survival has been observed in all groups with such cancers. These changes in survival indicate that treatment research, at least for the young cancer patients, has had a noticeable effect and that technology transfer has been successful.

The accomplishments in cancer treatment, particularly chemotherapy, have been especially significant. In 1965, there was no evidence that drugs cured cancer regularly. In 1980 the number of cancer patients cured of their disease by drugs was 46,000. While the numerical impact of this accomplishment may be modest, the change from essentially zero to 46,000 in 15 years represents a considerable advance. · The drop in our national mortality from cancer below age 45, when most drug-curable patients are found, tends to corroborate this estimate.

Several rates for patients receiving local treatment (surgery and/or radiotherapy) have also improved over the past 30 years. This is partly due to improvements in surgical techniques and surgical support (transfusions, antibiotics, etc.) but primarily to the widespread use of sophisticated and precise radiotherapy, equipment, and techniques. Largely as a result of advances in the concomitant use of radiotherapy and chemotherapy, surgery has become much less radical.

Improvements in the treatment of breast cancer should lead to decreasing breast cancer mortality, particularly in younger women. Changes in smoking habits and in the types of cigarettes smoked (lower tar and nicotine) should be followed by declines in the smoking-related cancers, including those of the lung, bladder, and pancreas. A flattening of the lung cancer mortality curve has been seen for white males, and the increase in the death rates for black males has not been increasing as sharply. For women, both black and white, however, the lung cancer death rate continues to increase rapidly.

For 1980, the overall five-year survival rate is estimated at 45 percent. It is important to note that this is based only on the 785,000 serious cancers. If the nearly 98 percent cure rate of the 445,000 more easily curable cases of skin and cervical cancer were included, the overall rate would be much higher.

Based on current incidence and survival rates there will be over 4 million former cancer patients alive in 1984. Thus, the United States must anticipate an increasing need for expert medical care, nursing care, aftercare facilities, rehabilitation programs, and other community and family activities necessary for the general societal integration of the increasing number of people who have survived their cancers.

Program Strategy

Due to limitations of manpower, knowledge, or funds, not all programs can be implemented simultaneously.

Currently the National Cancer Institute (NCI) is increasing its emphasis on research directed toward the prevention of cancer. At the same time, practical considerations dictate a reasonably high priority for research aimed at improved treatment of individuals who now have or will have cancer.

The following tenets serve as the basis for the program strategy of the National Cancer Program (NCP):

- Much of the knowledge crucial to the solution of cancer and other scientific problems is "fundamental" knowledge--i.e., derived from basic research.

- While the importance of fundamental research is a given, it is recognized that our mission requires us to plan and conduct a program in which applied research and developmental activities are also conducted where sufficient knowledge exists.

- Cancer is a worldwide problem, and much can be learned from the experience of other countries and the results of their research efforts. This requires the exchange of information among investigators throughout the world.

- It is important to develop a coordinated national program and to utilize all available resources, while seeking to minimize unnecessary duplication of efforts conducted by other participants in the National Cancer Program.

- It is important to foster the timely and practical application of research findings through technology transfer and appropriate education/demonstration programs.

Translating these tenets into a strategy for each of the three program components (Research, Control, and Resource Development) results in the following:

Research Strategy. Prevention is ultimately the most effective approach to the control of cancer. However, while knowledge is being sought to develop the means to prevent cancer, new cases of cancer will occur. Hence, cancer research must be two-pronged and develop effective management of disease for those who have the disease now and toward prevention for those who may develop the disease. Necessary for both these efforts is further knowledge regarding the control of cell growth and differentiation through basic as well as applied research.

Cancer Control (Applied Research) Strategy. Again the ultimate control of cancer is through prevention. Applied research in cancer prevention includes identification of optimal techniques to reduce exposure of individuals to known carcinogens, and/or to develop methods to interfere with the process of carcinogenesis after exposure has occurred (chemoprevention). Applied research in screening is desired to identify and promote safe, effective screening techniques that lead to early cancer detection. In the treatment area, cancer control efforts are being redirected to assure that community oncologists place patients on national research protocols. This participation will facilitate the diffusion of optimal diagnosis and treatment techniques to the general community, and further assure the patient resources necessary to complete large-scale clinical research efforts.

Resource Development Strategy. The goal in this area is to prevent or alleviate major shortages or deficiencies of resources critical to the operation of the National Cancer Program. The training of needed manpower, construction and upgrading of research facilities, and development of centers of scientific and clinical excellence are part of the overall strategy.

The goal of the National Cancer Institute is to develop the means for eliminating or controlling cancer. In order to achieve this, the NCI seeks to produce new knowledge, through a balanced effort encompassing a spectrum of fundamental research; the conversion of that new knowledge into practical applications through applied research and the subsequent promotion of effective applications through demonstrations and educational activities in cancer control; and through the development of needed resources, such as trained manpower and specialized facilities, to assure a continuing capability to carry out these activities.

Promising Areas of Research and Major Accomplishments

Areas of Research Holding Great Promise

Cancer Biology

- Monoclonal antibodies as tools for distinguishing various cell populations and for studying cell surface composition.

- Soluble factors which regulate differentiation of immature leucocytes and the functions of mature cells.

- Application of the knowledge that tumors consist of cell populations which can differ in fundamental characteristics (growth, antigenicity, drug sensitivity, and metastatic potential).

Cause and Prevention

- Prospective trials on prevention of many types of cancer through dietary manipulation or dietary supplements (vitamins, trace metals, etc.).

- Epidemiological studies to identify occupational and environmental causes of cancer.

- Construction of genetic linkage maps.

- *In vitro* bioassay systems for detecting carcinogens.

- A cell sorter that will permit quantitative measurement of surface markers by binding fluorescent reagents to cells.

Detection and Diagnosis

- Refinement of electronic X-ray image scanners suitable for computerized storage and analysis.

- Ultrasound probes inserted through endoscopes for imaging organs difficult to visualize with normal techniques.

- Development of contrast agents for ultrasonic imaging.

Treatment, Rehabilitation, and Continuing Care

- Second generation drugs.

- Particle therapy.

- Biological response modifiers.

- Radiosensitizers and radioprotectors.

- Use of hyperthermia and radiotherapy research.

Recent Accomplishments

Cancer Biology

- Increased knowledge about how eukaryotes control gene expression, thus eliminating need for bacterial studies in this regard.

- The ability to clone cancer cells and develop cells with specific behavioral traits permitting the study of processes previously limited by cell heterogeneity.

- Technical achievements in the area of somatic cell genetics, DNA cloning in bacteria and somatic cell hybridization, making it possible to use bacteria as factories for producing eukaryotic proteins, i.e., interferon, in quantity.

- The observation that some highly malignant mouse cancer cells have become normal, supporting the supposition that there are natural factors that can influence neoplastic progression. Some cancers can be reprogrammed to terminally differentiate.

Cause and Prevention

- RNA tumor viruses carry a gene for protein kinase that interferes with the normal cellular protein kinase cascade, thereby disturbing normal cellular metabolic processes.

- Using RNA tumor viruses, biochemical studies can be carried out on proteins which are responsible for the induction and maintenance of transformation.

- DNA from cells transformed by a chemical carcinogen, 3-methylcholanthrene, induces transformation when introduced into normal cells.

- Molecular mechanisms of chemical transformation may depend on activation of limited and unique pathways.

- Vitamin A and its analogues inhibit the process of transformation by chemicals and may become useful chemopreventive agents.

- Epidemiologic patterns have identified racial, occupational, and environmental risks to develop cancers.

- A functional DNA repair mechanism protects normal cells against transformation by radiation.

- A naturally occurring stimulator of cell division, epidermal growth factor (EGF), may activate a protein responsible for maintenance of the malignant state.

- Integration of an RNA tumor virus at a site adjacent to a specific cellular gene (SRC) enhances expression of that gene and leads to neoplasia.

- Normal cells may contain the genetic potential for becoming malignant.

- Newly-developed human tissue and cell-mediated tests are being used to screen for chemical carcinogens and to determine susceptibility among individual and/or target tissues.

- Monoclonal antibodies (hybridoma), because of their extreme specificity, can now be used as well-defined chemical agents:

  (a) To identify hormone receptors on human cells.

  (b) To identify tumor specific cell-surface antigens.

  (c) To discriminate between tumor virus antigens.

Detection and Diagnosis

- Radioactive labeling of antibody directed against tumor markers (CEA, hCG, αFP), demonstrating the ability to localize small tumors after intravenous injection.

- The identification of a gene that appears to be associated with a woman's risk to develop breast cancer.

- The building of a prototype of an electronic X-ray image scanner.

- The development of a pilot model for an ultrasound probe which can be used in conjunction with endoscopy.

- Major improvement in computerized tomographic imaging which enables imaging of the entire body.

Treatment, Rehabilitation, and Continuing Care

- A more rapid means of testing anticancer drugs (implantation of human tumor under the kidney capsule of a mouse and *in vitro* stem cell assay).
- Isolation of thymus cell growth factor that stimulates the growth of T cells from white blood cell cultures of patients with T-cell malignancies.
- Clinical studies showing that interferon has some anticancer effect.
- Increase in interferon supply through recombinant DNA technology.
- Further development of less toxic anticancer drugs, such as the Adriamycin analog, Aclacinomycin A.
- Further development of radiosensitizers and radioprotectors.
- Recommendations by consensus development conference on antiestrogen treatment in women found to have estrogen-responsive breast cancer.
- Development of particle therapy facilities at several Centers across the U.S.

FY 1982 Major Program Changes

Cancer Biology

- Studies of the effects of drugs and hormones on genetic expression by human cells *in vitro* will be initiated.
- The separation, identification, and systematic indexing of proteins found in humans will begin and their structure and presence in the human body will be correlated with the recurrence of specific diseases and disorders.
- New model systems will be developed to study the genetic aspects of cancer.
- The functions of "natural killer cells" in a patient's response to cancer will be studied.

Cause and Prevention

- Clinical trials to test the effectiveness of chemical and biological cancer prevention agents (chemoprevention) will be initiated.
- The interaction between environmental carcinogens and those genes in normal cells which are homologous to the transforming genes of viruses will be examined.

- Occupational studies to evaluate cancer risk among workers in petrochemical, automobile, leather, pharmaceutical, shipbuilding, and other industries will continue.
- Epidemiology studies to include collaborative projects with laboratory investigators to clarify the role of dietary and other exogenous factors that may affect the risk of cancer will be expanded.
- The relationship between cellular DNA repair systems and cell response to carcinogenic and chemotherapeutic agents will be studied.
- Efforts to develop rapid assay techniques, using human cells, for assessing environmental chemicals as carcinogens will continue.
- Research on the isolation, characterization, and mechanism of action of transforming genes and their protein products will continue.
- Trials to determine optimal smoking prevention and cessation methods for different population groups will not be initiated.

Detection and Diagnosis

- Clinical evaluation of new diagnostic technologies, such as the endoscopic ultrasound probe and electronic image recorder, will begin.
- Large scale human trials with radiolabeled antibody will be initiated.
- Lung cancer screening projects will continue. A detailed atlas on early diagnosis of lung cancer for physicians and the first report on lung cancer prevalence in the screened population will be completed.
- Trials to optimize the frequency of screening for breast cancer using low dose mammography will not be initiated.

Treatment, Rehabilitation, and Continuing Care

- Studies will be initiated on the spontaneous development of drug resistance in tumor cell populations and the design of therapeutic approaches to compensate for such development.
- Studies will be supported to investigate the modification of anticancer drug distribution, disposition, and metabolism resulting from the interactions of one drug with another.
- Basic studies will continue on the biochemistry and pharmacology of anticancer compounds as well as studies on cell kinetics and tumor biology of cancer therapy in experimental animals and cell systems.
- At least three Cooperative Agreements for establishing and supporting clinical cooperative groups that will serve distinct geographic regions will be funded.

- Clinical trials combining biological response modifiers with other more conventional modalities of therapy will be initiated.

- Developmental work to identify new and interesting biologicals in addition to the continued emphasis on several types of interferon will continue.

- Experimental systems to evaluate and select biologicals at the Frederick Cancer Research Center will be fully implemented.

- The priority and emphasis on surgical oncology research will be increased through the initiation of grants resulting from a request for applications.

- In the area of clinical trials, new and improved methods of treatment involving fewer side effects and minimum adverse effects on the patient will be explored. Work involving THC and its analogues as antiemetics will continue. Studies of therapeutic hypernutrition on tolerance to and effects of chemotherapy and combined modality therapy will be carried out.

- In the preclinical area, efforts to accumulate sufficient data to test the correlation between the *in vitro* stem assay and *in vivo* screening systems will continue. A project to test the correlation of the *in vitro* stem cell assay with clinical results will be initiated.

In addition to the 1982 program changes noted above, two programs which cut across the four categories of effort will not be initiated: modifying research laboratories to reduce biohazard risks, and improving the quality of cancer management in the community.

FY 1983 Major Program Changes

Cancer Biology

- Studies will continue, at the fundamental level, on the mechanism by which cells of the immune system interact with foreign biological materials.

- Studies of how hormones affect the activity of genes in mammary tissue, hopefully leading to information to help reduce risk of breast cancer, will be initiated.

- Investigations of the effects of changes in diet composition and control of food intake on tumor growth will be initiated.

- Molecular studies of the mechanisms by which cells become malignant and develop the ability to metastasize will continue.

Cause and Prevention

- Emphasis will be given to research defining specific enzymatic processes which metabolize chemical carcinogens.
- Recent findings that an aberration in the cell pathway, which transmits high energy pathway groups to the sodium potassium "pump," will be further investigated.
- Efforts to develop better and more effective methods of predicting carcinogenicity, mutagenicity, and teratogenicity will be expanded.
- Investigations of cellular and molecular mechanisms of carcinogenesis will continue.
- Studies of vitamin A derivatives as preventive agents will continue.
- Studies of radiation exposure and cancer will continue.
- New studies on the possible involvement between cancer and immunosuppressive agents, estrogens, and other hormones will be initiated.
- Studies of the interactive effects of chemical, physical, and biological carcinogenic and co-carcinogenic agents in cultured human epithelial cells will continue.
- Studies to determine specific metabolic pathways of carcinogen detoxification will continue.
- Studies on the genes which determine variations on individual susceptability to various carcinogens will continue.
- The role of the endogenous sarc genes as etiologic factors in human cancer will be investigated.
- Investigations of the molecular mechanism by which virus-coded proteins induce cancer will continue.
- Epidemiological studies to detect environmental and hereditary factors contributing to excessive occurrence of cancer in specific geographic locations, and on the role of nutrition and lifestyle in the cause and prevention of cancer will continue.
- Biochemical epidemiology studies to identify individuals at a high risk of cancer will be initiated.
- Research to identify the effects of low-level exposures to radiation will continue.
- The viral gene products (proteins) which are directly responsible for the induction of cancer will be isolated and characterized, and sensitive assays for their detection will be developed.

- Using molecular techniques, such as gene cloning and DNA sequence analysis, aberrations caused by carcinogens in the structure and function of normal genes will be studied in cultured human epithelial cells.

Detection and Diagnosis

- Cancer "marker" studies will continue, including the application of monoclonal antibody technology as a specific and accurate tool for cancer diagnosis.
- The immunodiagnosis program will be expanded to develop new immunologic reagents and methods for early cancer diagnosis.
- Some reprogramming could allow new efforts in the development of image intensifying agents.

Treatment, Rehabilitation, and Continuing Care

- Efforts to identify new biological response modifiers will be expanded.
- Clinical cooperative research will be expanded in order to assess the efficacy of biological response modifiers.
- A clinical trial of long-term nutritional support aimed at correcting and maintaining a normal nutritional status in the cancer patient during treatment will be initiated.
- Clinical studies involving the utilization of regional or local hyperthermia will be performed.
- Additional support will be given to cancer centers in order to allow planning for the clinical use of pi mesons and heavy ions in man.
- Chemoprevention clinical trials will be initiated to determine the mechanism of action as well as the efficacy of these agents.
- Efforts to assess the impact of in vitro drug screening will be carefully reviewed and adaptions exploited when possible.
- Phase I and II clinical evaluation of radiosensitizers and radioprotectors will be initiated.
- Phase III and IV clinical trials of biological response modifiers, especially newly identified agents, will be expanded.
- Increased support will be given to screening efforts in the drug development program.
- Studies of methods to prevent chronic adverse side effects of antitumor agents will continue.

- An investigation will be carried out in basic science mechanisms, both in vivo and in vitro, of radiation effects and their modification by pharmacologic agents.
- Studies will be initiated to examine the central nervous system pharmacokinetics of anticancer agents.
- Studies integrating Biological Response Modifiers (BRM's) into clinical oncology will be initiated. These will include the evaluation of BRM's at known effective doses in the surgical adjuvant therapy of cancer.
- Clinical data will begin to accumulate on drugs selected on the basis of activity in human tumor xenograft systems, allowing a preliminary evaluation of those screens. All of this information will be accumulated from initiatives started prior to 1983. At this budget level the ability to exploit their results will be hampered.
- Results expected from early clinical trials testing interferon in patients will begin to accumulate sufficient data for early evaluation.

Impact of Program Changes on 1983-85 Period

The continuation and expansion of existing programs and the initiation of others during FY 1982 and 1983 will have a significant impact on the three-year period 1983-85.

Basic studies conducted during FY 1982 and 1983 will lay the groundwork for a better understanding of the genetic aspects of cancer--i.e., regulation of genes that control cell growth, transforming genes, and definition of those genes which determine cancer susceptability. These studies will have broad application in the areas of cancer prevention as well as treatment.

The success of efforts begun in FY 1982 and 1983 to develop chemical and biological agents for the prevention of cancer will determine whether the chemoprevention program will be expanded during the 1983-85 period. Clinical trials initiated in FY 1982 should provide evidence of the effectiveness of these agents in the prevention of cancer.

Epidemiological studies, continued during the 1982-83 period, will be of high priority during the 1983-85 period. These studies always have the potential of discovering factors contributing to excessive cancer incidence. This knowledge could of course lead to elimination of those factors and a reduction in cancer incidence. Past studies have implicated exposure to asbestos during shipyard work in World War II as the explanation for the high rates of lung cancer in coastal areas, snuff dipping (smokeless tobacco) for the high rates of mouth cancer among females in the southern United States, and nutritional deficiencies and alcohol consumption for the high rates of esophageal cancer among black men in urban areas. The NCI also discovered a relationship between the use of menopausal estrogens and the risk of breast cancer, and confirmed the association between these agents and endometrial cancer. Reduced use of menopausal estrogens has resulted in a dramatic decrease in the incidence of this type of cancer.

Evaluations of several methods and technologies to detect and diagnose cancer will be completed during the 1982-83 period. The results of these evaluations as well as those of various screening and cancer "marker" programs should improve our ability to detect and diagnose cancer at its earliest stages, thus permitting more effective treatment.

Basic studies to characterize known biological response modifiers, begun in FY 1982, will enable the development of more effective methods to identify new ones. Results of clinical trials initiated during the 1982-83 period will indicate the effectiveness of this treatment and how it may be integrated with other therapeutic modalities.

By 1984 early results from clinical trials involving the high-LET radiation program will begin to provide data for an evaluation of this treatment as well as the utility of the equipment. The results of this evaluation will allow more effective planning for the clinical use of neutrons and other high-LET radiation and the development of these particle therapy facilities at several centers across the United States. These forms of radiotherapy have the theoretical advantage of being more effective in human tumors than standard radiotherapy.

NCI

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

DATE: FEB 19 1981

TO : Director
National Cancer Institute

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It is encouraging to note the resourcefulness of the NCI in adapting its program strategies to accommodate new demands within the constraints posed by constricted budgets. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

D S Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

In pursuing its goal to develop the means for eliminating or controlling cancer, the National Cancer Institute seeks to produce new knowledge, through a balanced effort encompassing a spectrum of fundamental and applied research; to promote the widest possible utilization of current knowledge through demonstrations and educational activities in cancer control; and, through the development of needed resources, such as trained manpower and specialized facilities, to assure continuing capability to carry out these activities.

Impact of Stabilization

- The total number of research project grants (R01s) will remain about the same in FY 1981 and increase slightly in FY 1982.

- The total number of program projects to be supported (P01s) will decrease slightly in FY 1981 and again in FY 1982. The number of competing P01s in FY 1982 will be less than half the number funded in FY 1980.

- The total number of research centers will drop slightly in FY 1981 and then remain the same in FY 1982 and 1983.

- The number of clinical education programs will decline sharply in FY 1981 and again in FY 1982 amounting to roughly half the number funded in FY 1980. This reflects an overall trend to reduce the training of clinical oncologists.

- The number of R&D contracts will drop sharply from 1980 levels in FY 1981 and moderately in FY 1982.

Ionizing Radiation/Radiation Biology

- The establishment of the low-level radiation program within NCI is continuing, and several contracts (interagency agreements) have been placed and several more are at different stages of processing. Up until now approximately $1 million has been committed in FY 1981. The establishment of a research grant program may have to wait until the administrative placement of low-level radiation has been decided upon; meanwhile, several program announcements in the area of low-level radiation effects are in preparation. The majority of radiation biology research grants (all levels) are currently in the Radiotherapy Development Branch, Division of Cancer Treatment (DCT), NCI. It is anticipated that projects for new research in the areas of biological effects of low-level radiation, will be identified and work initiated in FY 1982. (The establishment of a Low-Level Radiation Effects Branch was approved in early April 1981.)

National Toxicology Program

- NCI feels that NTP-sponsored routine testing should be performed only on a very few highly selected chemicals for which there is an overriding public health concern and no private sector sponsor.

Biological Response Modifiers Program (BRMP)

- Interferon is prominent among the several substances made by the body which offer hope of altering its response to cancer. A current goal of the BRMP is to investigate the potential therapeutic efficacy of interferon in the treatment of cancer. Clinical trials supported by the NCI are under way in seven institutions and it is expected that an appropriate dose and level of tolerance for a variety of interferons will be known in 1981.

- The Division of Cancer Treatment, responding to the House Appropriation Committee's request, has prepared a report which summarizes the NIH funding for interferon at $16.0 million and for other biological response modifiers (BRM) at $23.9 million (total $39.9 million). The NCI funding is $8.6 million for interferon and $23.9 for other BRM's (total $32.5 million).

- Two additional biological response modifiers will be evaluated this year: (1) thymosin, and (2) MVE-2, a synthetic substance that stimulates the immune system.

Division of Resources, Centers, and Community Activities (DRCCA)

- The operational strategy for the new DRCCA will combine cancer control programs, centers, and resource development activities, enlarge the role of research in cancer control activities, and implement new programs in the area of applied prevention. An outcome of this new strategy should be to generally upgrade the quality of cancer care in the community. In implementing this strategy, special attention will be given to the impact of these changes on ongoing cancer control activities and cancer center operations and to the views of private medical oncologists and their patients who will be asked to participate in national clinical research programs.

Research Opportunities

- In Cause and Prevention, NCI plans to initiate clinical trials to test the effectiveness of chemical and biological cancer prevention agents in interrupting the cancer causation process (chemoprevention).

- In Treatment, Rehabilitation, and Continuing Care, NCI plans to initiate new studies investigating the use of biological response modifiers in the treatment of human malignancies. Clinical studies show that interferon has some anticancer effect, possibly by inducing endonuclease activity. The techniques of gene splicing and recombinant DNA hold promise of increasing the supply of interferon.

- In the area of Detection and Diagnosis, the application of hybridoma technology holds promise for earlier detection of tumors and initiation of immunotherapy and for studying cellular changes in carcinogenesis.

- The use of recombinant DNA technology and other techniques for cell transformation continues to expand our understanding of the potential molecular and metabolic differences separating malignant from normal cells.

Biological Response Modifiers Program

Statement of Issue

The House Appropriations Report (96-1244) requested a report from the Director, NIH, at the 1981 hearings which would include: (1) how much of FY 1981 NIH funds were spent on research related to interferon and other biological response modifiers, and (2) a summary of their effect, insofar as is now known, in the treatment of cancer and viral disease.

In addition to providing the Congress with the information requested, the major issue is to demonstrate that the NIH/NCI efforts in this area of research have been timely and appropriate and have produced a well planned, organized, and balanced program in terms of content, the levels of investment in dollars and other resources, and the pace of the work.

Discussion of Issue

The NCI Biological Response Modifiers Program is a broadly based program which was initiated following an extensive review of the state of the art and the development of a comprehensive set of recommendations by a subcommittee of the DCT Board of Scientific Counselors. The subcommittee also recommended an integrated logical program plan similar to the Linear Array used successfully for the chemotherapeutic agents.

Although the immediate goals of this program are therapeutic, the scientific basis of biological response modification must be extensively explored to: eliminate arbitrary choices of preparation and dose; provide more specific and potent products for the future; and provide the necessary information required for the utilization of agents now available and for the development of future approaches.

The program has initiated several sets of projects: (1) procurement of various types of interferon for clinical trials and experimental studies, and (2) initial clinical studies involving interferons, thymosin fractions, and MVE-2, an interferon inducer derived from pyran copolymer. Although any significant clinical results could heighten community pressures to produce more interferon and to use it more widely, NCI intends to carry out this more broadly based program.

The Division of Cancer Treatment has prepared a report (dated Dec. 12, 1980), responding to the House request, which summarizes NIH funding for interferon as 16.0 million and for other biological response modifiers as $23.9 million, for a total of $39.9 million. The NCI funding is $8.6, $23.9, and $32.5 million, respectively.

There have been some brief responses in patients with breast cancer, multiple myeloma, melanoma, and lymphoma, most often in patients with soft tissue involvement. While these responses are not major when compared with combination chemotherapy and radiation therapy, they are significant since they are being seen with interferon, a totally new type of anticancer treatment.

Interferon has produced some toxicity, and some patients have experienced fever, fatigue, weight loss, lowering of blood counts, and partial hair loss. These side effects have often become less troublesome with continued treatment, which may indicate that the dosage can be increased over time.

The National Institute of Allergy and Infectious Diseases is conducting clinical trials of interferon in chronic hepatitis B due to hepatitis B virus. Interferon apparently has beneficial effects and may eradicate the virus in some cases. Interferon has also been given to patients undergoing trigeminal nerve resection for the painful "tic douloureaux syndrome" and has been found to prevent the reactivation of herpes infection in the nerve, a frequent complication. It has also been found to be beneficial in the treatment of shingles or herpes zoster virus infection in cancer patients and is under study in the therapy of other herpes virus infections.

Alternatives and/or Suggested Position

NCI will continue to carry out this program as developed by the DCT Board of Scientific Counselors Subcommittee. Funding is currently adequate to explore most of the promising leads. With decreased support, there will necessarily be some internal program reallocation of funds which will affect program balance.

The program can be expanded in a productive way to pursue all promising leads, especially the testing of the many new compounds being offered by pharmaceutical companies. If positive results are obtained, NCI would like the option of requesting additional monies to take advantage of new developments in the Biological Response Modifiers Program.

Operational Strategy for DRCCA

Statement of Issue

The new Division of Resources, Centers, and Community Activities (DRCCA) will implement an operational strategy that will: integrate control, centers, and resource development activities; enlarge the role of research in cancer control activities; and implement new programs in the area of applied prevention. The issue is the impact that this significantly different strategy will have on: (a) ongoing cancer control activities and cancer center operations; (b) some members of the Congress who were instrumental in expanding the number of cancer centers and initiating the Cancer Control Program as part of the NCP; and (c) private medical oncologists and their patients who will be asked to participate in national level clinical research programs.

Discussion of Issue

The new strategy will have two immediate thrusts: (a) Generally upgrade the quality of cancer care in the community. The number of medical oncologists who have been trained in research centers and who are now in private practice is now sufficiently large so that they should become effective agents for improving the quality of medical management across the continuum, including prevention, detection, diagnosis, pretreatment evaluation, treatment, rehabilitation, and continuing care. To facilitate change in the diagnosis and treatment segments, community physicians and their patients will be incorporated into national level cooperative clinical research programs. This will improve the quality of care for these patients placed on protocol, will probably also improve the quality of care for nonprotocol patients treated by these physicians and at the same time, will increase the flow of patients to clinical research programs. Two potential problem areas: reluctance of some private physicians and/or their patients to participate in Federal "research" programs; negative reactions from established cancer centers and university medical centers which have traditionally been the focal points for these activities. (b) Applied Prevention. This area will include three major activities: (1) the planning and implementation of a research and development effort in chemoprevention to either substantiate or negate the small body of information which indicates the possibility of interfering with the process of carcinogenesis after-the-fact; (2) the expansion of research and development activities involving known carcinogens (e.g., behavioral research to develop improved smoking cessation approaches for teenagers); and (3) the planning and implementation of screening programs primarily in those areas with high impact (e.g., studies to determine the frequency of mammography for both maximum safety and diagnostic effectiveness).

Alternatives and/or Suggested Position

The new strategy is an alternative to previous operations and is deemed to be more effective and productive in achieving the expanded mission of the new division, and also in providing for an expanded role for the private physicians and their patients in national research programs. The NCI considers this position as the policy of the Institute concerning the operations of DRCCA.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Director's Overview

The National Institute of Child Health and Human Development (NICHD) is unique among the eleven Institutes of the NIH because of its emphasis on biological and behavioral research focused on prevention of developmental problems and the diseases and disorders that arise from them. The Institute's program addresses the following problems:

- Each year more than 45,000 infants die in the United States, most of them from birth defects or infections, or because they are of low birth weight.
- Seven of every 100 infants born alive have physical or mental handicaps that will last a lifetime.
- Moreover, one in every five births, some 700,000 births each year, is unwanted.
- Two million couples who want to have children are unable to have them.

Such problems are costly. A 1978 study indicated an estimated average cost of over $8,000 for intensive care of each premature infant or an annual estimated hospital cost of over $1.5 billion. The cost of birth defects is estimated at a minimum of $2.5 billion a year for hospitalization, physicians' fees, and services.

Much of the work of the NICHD is aimed at understanding normal human development and processes--the transformation of a fertilized egg into an infant; the growth of an infant into a productive, healthy adolescent and adult; and the complexities involved in contraception, childbearing, and childrearing. Elucidation of human development is an intriguing and profound challenge of modern science. Moreover, concentration on early development, when many diseases and disorders originate, places the NICHD in a prime position to contribute to preventive medicine.

Pregnancy

The infant death rate in the United States has dropped dramatically since the 1950s because research has shown us how to save more babies of very low birth weight. But decreases have not been achieved in all weight categories, and 13 countries still have lower infant mortality rates than the United States. Investigators supported by the NICHD are learning how to prevent prematurity and low birth weight by studying why labor begins and how the mother, via the placenta, nourishes the fetus. Understanding the complex interactions that take place between the mother and the fetus during pregnancy and labor forms the basis for improving medical management of pregnancy and examining new drugs to delay early labor.

Fetal Medicine

Advances in the past decade in understanding the developing embryo and fetus have been paralleled by breakthroughs in the technology used in prenatal diagnosis. These gains give us the knowledge needed to begin correcting problems *in utero* and preventing many disorders before birth.

Recent success in the management of diabetic pregnancy is an example of how knowledge about fetal development contributes to prevention of death and disease. Improvements in the management of diabetic pregnancy have been such that the risks to the mother are now very low and the number of babies lost has dropped to about the rate in uncomplicated pregnancy. Additional research is needed, however, since this improvement has not been matched by a decrease in congenital defects associated with maternal diabetes.

With advances in technology offering safer direct access to the fetus, comes the hope that more problems can be prevented before birth. In animal models, for example, it is now possible to prevent by drug therapy or hormone replacement certain defects of the eye, the palate, and the genitals. The ability to treat the embryo or fetus *in utero* depends upon a fundamental understanding of the mechanisms and timing of developmental processes, and it is in this basic area that the NICHD plans to concentrate research support in the future.

Mental Retardation

About 6.6 million people in the United States are mentally retarded and the number increases by 126,000 new cases each year, occurring in 5 percent of all births. This disorder, which lasts a lifetime and costs at least $10 billion per year in public funds, is caused by biologic, social, or psychologic factors or is due to a combination of factors. Whatever its causes, it is clear that the roots of mental retardation lie in the faulty early development of neurobiologic mechanisms. Therefore, some of the most important research supported by the NICHD is the study of the maturation, migration, and interconnection of the 200 billion neurons that are generated during the first three months of fetal existence. These studies hold great promise for answering some of the most important questions relating to brain development.

Studies in Children

As a result of Institute-supported research since 1972, significant progress has been made in understanding the sudden infant death syndrome (SIDS)--the leading cause of death among infants between the ages of 1 and 12 months.

Data from a current NICHD study make a genetic origin for SIDS seem unlikely, providing strong support for continuing research on environmental and developmental causes of SIDS.

Children with dwarfism because their pituitary glands produce insufficient human growth hormone will be the first beneficiaries of recombinant DNA technology, a technology pioneered by NICHD scientists and investigators working elsewhere.

Contraception and Reproduction

Because of the widely publicized reports on the possible association between the use of oral contraceptives and heart attack, stroke, and certain benign tumors, many women have stopped taking the pill and are turning to barrier methods of contraception. Therefore, the Institute is supporting clinical trials on the cervical cap, a barrier method of contraception currently unavailable in this country, but reportedly easier to use and more effective than the diaphragm. Also underway is a clinical trial to compare a new contraceptive sponge diaphragm to diaphragms currently available.

Improved drug delivery systems are also being sought. Oral contraceptives are currently taken in a pill form that results in rapid absorption of the drug. The rapid absorption produces levels of drugs in the blood higher than necessary for contraception. Methods that would release these drugs into the blood in a slower, more sustained fashion should improve safety of available drugs.

The Institute will expand somewhat its studies on infertility in FY 1982, both through research in its Bethesda laboratories and through research grants. An NICHD investigator working with monkeys recently developed a procedure that permits pregnancy in females with blocked fallopian tubes.

The problems addressed by the NICHD are among the most significant and costly health problems of our society. Answers to these problems can be found in research directed toward fundamental questions in human development and reproduction. The NICHD research program could have great impact on health care expenses in this country because the diseases and disorders we seek to prevent are lifelong problems, some of the most costly to the Nation.

FY 1981--Examples of Areas of Research Holding Promise for Progress and/or Major Advances

- The NICHD supports the largest program in the world for the synthesis of modified copies, or analogs, of luteinizing hormone-releasing hormone (LHRH). LHRH stimulates the pituitary gland to secrete other hormones that regulate the functions of the ovary in women and the testis in men. These analogs could herald the development of a new generation of contraceptives that are effective and safe for both men and women. They have already been used successfully to treat infertility in women, and may be useful for male infertility as well.

- Recent data indicates that normal development of the electrical activity of a human brain can be characterized. Equations have been established that predict electroencephalogram results in normal children aged 5 to 15 for four areas of the brain that are important to learning. To the extent that neuroelectric data can be established to describe the development of the central nervous system, it can be collated with behavioral and learning milestones and chronological age and thereby help identify children who have a potential for learning disability.

- Each year, about 100,000 babies are born whose growth is retarded in the womb. An animal model of the nutritional aspects of intrauterine growth retardation (IUGR) has been developed with NICHD support. This model, which utilizes fetal sheep, effects IUGR by embolizing the lateral side of the placenta and by restricting maternal intake of protein and calories. In FY 1983, the Institute plans to use this animal model to determine the feasibility of intrauterine nutritional therapy to augment the rate of fetal growth.

- Investigators have obtained evidence that bacteria that cause urinary tract or vaginal infections during pregnancy contain high levels of phospholipase A2. Human phospholipase, an enzyme found in amniotic membranes, is thought to initiate labor normally. Bacterial phospholipase from maternal infections may be responsible for premature labor. Other investigators have documented a relationship between urinary tract infections and decreased infant birth weight. Research on these findings will include epidemiological studies, primate studies, and clinical trials to assess whether treatment can reduce the incidence of premature labor.

- A recently completed study has shown that both current and long-term past oral contraceptive use increase the risk of myocardial infarction. Three recently completed studies of the influence of oral contraceptive use on the occurrence of hypertension are being evaluated, and several studies are in progress to elucidate the mechanisms by which oral contraceptive use increases the risk of cardiovascular disease. These include studies of the possible role of antibodies to ethinyl estradiol, and studies of the effects of different oral contraceptive formulations on lipoprotein patterns.

- Research on family and household demography indicates that there is a widening divergence between the two concepts. Families that relate to more than one household are increasing and conversely, households that contain family fragments or relate to more than one family (as in the case of remarriage after divorce involving one or more children from the previous marriage) are becoming more numerous. These changes materially alter the living arrangements of the American population, the environment in which fertility decisions are made, children are raised, and general health is promoted and maintained.

- Institute-supported investigators have succeeded in developing a mouse model for genetic disorders with particular emphasis in trisomy 21 (Down's syndrome). Three of the genes known to be on human chromosome

21 have been "mapped" on mouse chromosome 16. This observation suggests a genetic homology between human chromosome 21 and mouse chromosome 16. The development of such an animal model will permit a detailed developmental, biochemical, and morphological analysis of the pathogenesis of congenital defects which will either be difficult or impractical to carry out in human subjects due to ethical or scientific considerations.

- Research by NICHD investigators on recombinant DNA techniques has enabled the production of human growth hormone (hGH) in large quantities. NICHD support has also determined that 15 percent of children with normal variant short stature (NVSS), about 7,500 children per year, will respond to therapy with hGH, even though immunoassay tests indicate that their hGH levels are normal. The hormone is not secreted, however, in a form that is clinically active. In anticipation of the availability of hGH in large enough quantities, the Institute plans include research to develop blood tests for NVSS and to identify abnormally aggregated polypeptide hormones in other related conditions such as the delayed onset of puberty.

- Advances in cerebral neurochemistry have indicated that much more is involved in the development of obesity than just overeating or lack of exercise. The drive to overeat depends on concentration and functions of several kinds of neurotransmitters in the hypothalamus, including serotonin, acetylcholine, dopamine, and neuropeptides such as bombesin, endorphins, and cholecystokinin. These hypothalamic neurotransmitters affect thermogenesis and energy metabolism as well as appetite and therefore determine the amount of caloric intake stored as fat. These advances in the neurochemistry of obesity provide targets for possible pharmacologic intervention, especially in cases of severe obesity.

- It has been found that the ability to learn how to read is closely related to the ability to acquire facility in the use of language, and that children who exhibit early problems in language acquisition are very likely to have similar problems in learning how to read. These findings need to be followed up by further research for they have important implications for the diagnosis and prognosis of reading disability (dyslexia), as well as the prevention or remediation of the disability.

- Recent research has documented the fact that early and continuing social interaction between the infant and its mother, as well as adequate sensory stimulation--tactile, auditory, and visual--are required if the infant is to develop normally. These findings are being successfully applied to provide more optimum contact between mother and child while still in the hospital, particularly in the case of prematurely-born infants who must be placed in intensive-care nurseries. Further research to apply these findings to children suffering from other forms of early developmental disability is now called for.

- It has been observed in the frog that adult specialized nucleii of the kidney, heart, skin, and lung can be transplanted successfully to enucleated frog's eggs which can then form feeding frog tadpoles. Such nuclear transplantation has now been achieved in a mammalian model (mouse) resulting in live born mice derived exclusively from the transplanted nucleii. Using these techniques it may become possible to correct maldevelopment in the human egg or to replace damaged or diseased tissues and organs in the adult.

FY 1982 Program Changes

FY 1982 is essentially a no-growth budget year. The intent to stabilize the base of investigator-initiated research grants limits the Institute's ability to develop new programs and initiatives. Only 378 competing research project grants will be awarded which is 10 fewer than FY 1981. Other support mechanisms, including research centers and research training, will remain at or near the FY 1981 level. Major program changes are not planned for FY 1982. In order to maintain activity across the Institute's 10 areas of program emphasis, some significant breakthroughs will not be pursued.

Cutbacks and Program Delays

It will not be possible, for example, to expand the science base in reproductive sciences nor will the Institute be able to initiate its program of research on reproductive diseases.

Clinical trials will be postponed in areas critical to research on the prevention of prematurity. It will not be possible to initiate needed studies on screening and treatment of subclinical genitourinary infections in pregnant women or on the management of complications of pregnancy and labor. A major study on diabetes and pregnancy which is focused on reducing the risk of congenital malformations among offspring, will not be expanded as planned.

Promising research on congenital defects will be curtailed. Basic studies in genetics and developmental biology will not be supported and new research on normal and abnormal limb development will be postponed.

The decrease in projected levels of funding will delay contraceptive development studies on the safety assessment of LHRH analogs and long-acting injectibles and on the development of improved spermicidal preparations (barrier methods). It will also not be possible to expand the drug synthesis and testing program.

The reduction would affect the development and support of the Population Research Centers Program with a corresponding reduction of research and training in the social sciences related to population.

Plans to exploit the new models on etiology and nutritional therapy of intrauterine growth retardation (IUGR) will be delayed. Clinical trials on the newly available human growth hormone (hGH) manufactured by bacterial clones will be postponed as will plans to develop special hGH tests for the diagnosis of normal variant short stature.

Program Expansions

By decreasing and holding other areas level, additional research can be supported in child and adolescent development to pursue areas identified as being of high promise. These include: the collection of normative neuroelectric data relevant to learning and other behavioral factors during development; the relationship of reading acquisition and language acquisition and the role of early social interaction between mother and infant in normal development.

New Initiatives

Research on contraceptive evaluation must be responsive to newly emerging questions of safety and health. In FY 1982, new research is planned to investigate mechanisms by which the use of oral contraceptives increases the risk of cardiovascular disease. Studies also will be initiated to evaluate whether surgical sterilization has any long-term influence on a woman's health. New studies are planned to evaluate whether exposure to spermicides influences the occurrence of (1) birth defects, and (2) venereal disease.

FY 1983 Program Changes

At this level, modest program growth can be realized.

- Studies can begin on reproductive diseases in men and women. Specifically, research is planned on the etiology and amelioration of endometriosis. Research planning workshops will be held on male gonadal dysfunction and on immune diseases of reproductive tissues.
- Research will increase on animal studies of *in vitro* fertilization and embryo transfer, on the development of hybridomas, and in fundamental studies on reproductive neuroendocrinology and gonadotropin releasing hormone.
- Animal safety studies and Phase I clinical trials can be undertaken on LHRH antagonists and new long-acting injectable progestin.
- New research on contraceptive development will include clinical trials on the utilization of natural estrogens and the development of new more precise methods to use in natural family planning and fertility awareness.
- Studies will begin on the reversibility of surgical sterilization in men and women.
- Mechanisms by which intrauterine devices increase the risk of pelvic inflammatory diseases will be investigated. Determinants of variation

in the use-effectiveness of spermicides and other barrier contraceptives will be studied.

- Social and behavioral research in population sciences will be expanded. Studies will increase on decision-making and consequences involved in the postponement of childbearing. Female labor-force participation will be examined for its impact upon the family and upon fertility. Sex differences in mortality and morbidity will be elucidated.

- The fragile X syndrome is the most frequent genetic cause of mental retardation in males. Projects on this syndrome will be encouraged with emphasis on its epidemiology, clinical manifestation, and the tissue culture conditions that will facilitate demonstration of the abnormal X chromosome among affected subjects and female carriers.

- Biological bases of behavioral development will be investigated with emphasis on the role of neural plasticity and lateralization of brain function during development. Early experience, particularly for infants who survive a high risk birth, will be evaluated for its impact on subsequent developmental delays.

- As a result of the NICHD 1979 conference, "Women, A Developmental Perspective," new research will be supported on male-female differences in behavioral development. This area, after a long period of neglect, has undergone rapid expansion. Recent studies have raised controversies on such subjects as the possible involvement of genetics as a cause of sex differences in mathematical achievement and the higher incidence of reading problems in boys than girls. These issues need to be addressed by research.

- The congenital defects research program will be expanded to include studies on drugs, maternal conditions, and intrauterine infections that have been identified as potential causes of structural malformations. Of special concern is the immunologic vulnerability of premature infants and newborns to infections and the development of improved therapy for neonatal septicemia which is a leading cause of infant morbidity and mortality.

- Studies will be concentrated on limb development, not only because of the severity and incidence of congenital defects in this area, (223.8 per 100,000 live births) but also because it is a model for better understanding of the roles of hereditary and environmental factors on birth defects and skeletal dysplasia. Specific studies of hereditary and induced deformities will be used as a valuable means to provide understanding of the extent of repair and regulation possible in the developing limb.

- Exposure to ultrasound during embryonic development will be evaluated to identify possible harmful effects.

NICHD

- Analysis of the data from the NICHD cooperative multicenter study of SIDS will be completed in 1982 and is expected to identify specific factors that place infants at high risk. It is anticipated that the results will suggest specific studies that need to be done to apply intervention strategies to high risk infants to see if the incidence of SIDS can be reduced.

- A research conference would be held with the cosponsorship of the NINCDS and NIAID to evaluate the use and efficacy of screening tests for infection (Toxoplasma, Cytomegalovirus) during pregnancy.

- New methods for managing the diabetic condition early in pregnancy--during the time that fetal organs are formed--will be tested for effectiveness in reducing the risk of congenital defects among offspring.

- The study of biological and social impact of teenage pregnancy and childbearing will be expanded.

- The effects on mother and fetus of exposure during pregnancy to pharmaceuticals, teratogens, and environmental hazards will be assessed.

- The outcome of pregnancies with various complications of labor and the long-term outcome of very low birth weight infants will be evaluated.

- New improved methods for diagnosing developmental defects in utero will be sought. Efforts will concentrate on developing accurate tests to confirm results of screening for neural tube defects.

- A marked reduction has occurred in the infant mortality rate in the United States in the last ten years. There has, however, been relatively little change in the rate of low birth weight in this country which still contributes approximately 75 percent of the infant mortality rate. Therefore, a study has been started in the Washington, D.C., area which has a very high rate of infant mortality, that will focus specifically on the identification of factors, conditions, and circumstances that increase substantially the risks of having a low birth weight child. Once these factors and conditions are identified, new strategies for intervention may be designed to reduce the risk of low birth weight.

- Studies will continue of infant feeding practices in different cultural groups and the effect of these practices on the health of the infant during the first year of life. Additional research on the process (biological, social, and behavioral) leading to successful breast feeding is planned to help women desiring to breast feed who are unsuccessful in their attempts.

- New program initiatives will be undertaken in developmental gastroenterology, specifically on the developmental immunology of the gut, gastrointestinal growth factors, and transport and absorptive capabilities in newborn and premature infants.

NICHD

- Epidemiologic research will be supported to determine whether risks for intrauterine growth retardation can be predicted. Studies will be encouraged to develop ultrasonographic standards for fetal growth.

NICHD

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Institute of Child Health and
Human Development

DATE: MAR 5 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I was pleased to learn that the NICHD is developing a five year research plan to guide program development. It is encouraging to note that the plan will consider the resources that will be required to implement the recommendations. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

During the period of this plan, NICHD will focus biomedical and behavioral research on perinatal and infant nutrition, normal and abnormal fetal development, child and adolescent development, mental retardation, and problems of pregnancy and birth. Research will also be continued on human fertility and infertility, contraceptive development and safety, and causes and consequences of population change.

Impact of Stabilization

- The total number of research project grants to be supported in 1981 and 1982 will decrease slightly from the level that was supported in 1980; however, the number of competing awards to be made will increase moderately to reach the stabilized level.
- The number of research centers will remain the same in 1981 and 1982.
- Support for research training will be reduced in 1981. Support will be increased in 1982 although it will remain below the 1980 level.
- Research and development contracts will be maintained at essentially a constant level of effort. Any reductions in contracts would have an adverse impact on the population research program, specifically in contraceptive development and evaluation.
- Intramural research will remain stable in 1981 and 1982.

Five-Year Plan

- The NICHD is developing a Five-Year Research Plan which describes the state of science in the areas of concern to the Institute, identifies gaps in current knowledge and opportunities for promising studies, indicates future directions in which program development should proceed, and considers resources required to achieve the goals and objectives described in the Plan. The Plan has been undertaken by the staff of NICHD with the aid of outside consultants and a support contractor. The Institute expects to present the Plan to the NICHD Advisory Council in September 1981.

Research Centers

- The NICHD provides support for 26 population research centers, 12 mental retardation centers, and 7 perinatal centers. In 1981, approximately $25 million will be devoted to the support of centers.

- The review of center grant applications has been separated organizationally within the NICHD from the ongoing management of the center grants program.

Legislative Authority

The authority for the NICHD program on population research is now provided under Title X of the Public Health Service Act. This authority must be renewed in the next session of Congress. The NICHD believes that the authority for the conduct and support of research in this area should be repealed and once again placed under Section 301.

Research Opportunities

- Evidence indicates that bacteria associated with urinary tract or vaginal infections during pregnancy contain high levels of phospholipase A2 which may be implicated in the initiation of premature labor. Urinary tract infections have also been shown to relate to decreased infant birth weight. Research will be conducted to follow up on these findings.

- The etiology of 65-70 percent of all congenital defects is still unknown. Clinical studies are planned that combine developmental biology and developmental genetics in an effort to use newly developed techniques such as cell cloning, recombinant DNA, and immunoclonal antibodies to advance knowledge on the causes and prevention of birth defects.

- An animal model of the nutritional aspects of intrauterine growth retardation (IUGR) has been developed. This model effects IUGR by embolizing the lateral side of the placenta and by restricting maternal intake of protein and calories. The Institute plans to use this animal model to determine the feasibility of intrauterine nutritional therapy to augment the rate of fetal growth.

- The Institute is initiating a clinical trial as a first step in evaluating the use of human milk and components of human milk in the nutritional management of premature and low birth weight infants.

- Studies will be conducted on reproductive diseases of women such as endometriosis, dysmenorrhea, and polycystic ovarian syndrome. Additional studies will focus on disorders of men, particularly on prostatitis, prostatic hypertrophy, and varicocele.

- The development of recombinant DNA techniques has enabled the production of human growth hormone (hGH) in large quantities. In anticipation of the availability of such quantities of hGH, the Institute is planning research to develop blood tests for normal variant short stature (NVSS) and to identify abnormally aggregated polypeptide hormones in other related conditions such as the delayed onset of puberty.

- Studies in contraceptive evaluation will be initiated to: (1) determine whether there is substantial variation in steroid blood levels in women taking oral contraceptives; (2) evaluate the use-effectiveness of barrier contraceptives; and (3) investigate the reversibility of male sterilization and the factors involved in the restoration of fertility.

Action Items

Mr. Bruce Carson, Deputy Associate Director, OPPE, will prepare a list of all expiring legislative authorities and a statement of the NIH position concerning the renewal of each of these authorities. This should offer the NICHD an opportunity to examine and propose a reconsidered approach to the renewal of Title X.

NICHD

Title X

Statement of Issue

Title X of the Public Health Service Act: The authority for family planning and population research must be renewed in the next session of Congress.

Discussion of Issue

- The new Administration must act quickly to move a legislative proposal through the OMB.
- Congressional committee structure and membership has changed substantially in the Senate.

Alternatives and/or Suggested Position

- Repeal Title X sections dealing with research.
- Use Section 301 of the PHS Act as authority for population research.

HHS Initiative

Statement of Issue

"Population Research" has been identified as an initiative in the HHS research planning effort.

Discussion of Issue

Further development of this initiative is possible but will not proceed until more definitive information is available on the 1982 and 1983 budgets, as well as on the plans for continuation of the "Initiatives" planning effort.

Alternatives and/or Suggested Position

The current population research initiative would be updated and improved if circumstances changed sufficiently to warrant it.

PROGRAM PERFORMANCE SUMMARY

FERTILITY AND INFERTILITY RESEARCH

Program Description

Research on reproductive biology is encompassed within NICHD's program emphasis area entitled "Fertility and Infertility." Studies in this area provide knowledge on the processes of human reproduction, fertility regulation, and the treatment and cure of reproductive diseases and disorders. Studies on fertility and infertility are subsumed under the four major disciplines that comprise the reproductive sciences: (1) reproductive endocrinology, (2) reproductive biology, (3) reproductive medicine, and (4) reproductive chemistry.

Reproductive endocrinology includes the secretion, action, and metabolism of the reproductive hormones and the endocrine glands that secrete them. Reproductive biology includes reproductive processes and events such as oocyte maturation, sperm production, ovulation, sperm maturation, sperm capacitation, gamete transport, fertilization, early embryonic development, implantation, reproductive behavior, and nutrition in animals. Reproductive medicine includes human nutrition, human infertility, human reproductive diseases and disorders, andrology, and clinical studies of human reproduction. Reproductive chemistry includes the synthesis of reproductive peptides and steroids and isolation and purification of substances involved in reproduction, and the chemical modification of substances involved in reproduction for increased efficacy and diminution of undesirable side effects.

Legislative History

From its beginning in 1963, NICHD has put emphasis on programs in reproductive sciences to provide a science base for reproductive biology and for the study of human fertility and infertility. In 1968 the Presidential health message to Congress contained the mandate that established the Center for Population Research (CPR) within the Institute. The Center is responsible for the primary Federal effort in population research.

On December 24, 1970, Public Law 91-572 added a new Title X to the Public Health Service Act and authorized the promotion of research and research training, via grants and contracts, in the biomedical, contraceptive development, behavioral, and program implementation fields related to family planning and population. This authority was delegated by the Secretary, HEW, to NICHD to be administered by the Center for Population Research.

A principal change to Title X came through Title II of Public Law 94-63, the Family Planning and Population Research Act of 1975 (July 29, 1975). This broadened the authority to include the "conduct" as well as support of population research and required that Title X be the sole authority for population research appropriations. The Conference Report describes the new provision as intended by Congress to make clear that the entire population research effort of the Department be conducted under Section 1004 of the Public Health Service Act; the provision was not to be used to reduce the appropriate program support level for population research.

Current Legislative Status

Public Law 95-613 of November 8, 1978, extended authority for research activities in the fields related to family planning and population, with authorizations for fiscal years 1979 through 1981.

In the Omnibus Budget Reconciliation Act of 1981, which was signed into law on August 14, 1981 (specifically, Title IX--Health Services Facilities, Subtitle D--Categorical Programs, Family Planning Programs, Sec. 931(b)(2)), sections of 1004(b)(1) and (2), the specific authorization for population research and the prohibition on the use of funds for such research other than those appropriated under this section, were repealed. Section 1004(a), which describes the research, was not repealed.

It is the intent of Congress, according to the Conference Report on this measure, that:

> "the repeal of sections 1004(b)(1) and (b)(2) shall not operate to terminate the existing program of research and training conducted at the National Institutes of Health (NIH) under the authority of section 1004, or substantially modify its breadth of scope. The NIH has sufficiently broad authority under sections 301 and 441 of the Public Health Service Act to continue the existing human reproduction research and population research and training program, and it is the intention of the Conferees that such authority be exercised in this manner."

Reproductive Sciences Branch, FY 1979-82*
(In Thousands of Dollars)

	1979	1980	1981 est.	1982 est.
Research Projects				
R01	$28,208	$31,585	$35,760	$37,856
P01	1,481	1,911	2,177	2,313
Other Research Projects	--	--	215	387
Subtotal, Research Projects	29,689	33,496	38,152	40,556
Centers	7,749	8,042	8,393	9,075
Other Research	1,103	1,201	1,014	1,092
Contracts	--	--	--	--
Training				
NRSA	2,222	2,666	2,176	1,682
Others	--	--	--	--
Total	$40,763	$45,405	$49,735	$52,405

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*FY 1978 data available.

Research Plan--Fertility and Infertility

Program Objectives and Activities for Fiscal Year 1983

Fundamental Science Base. Program goal: To support investigator-initiated research in the reproductive sciences of highest scientific merit in order to establish and maintain the minimum fundamental science base required for the achievement of the remaining program goals. (Fiscal Year 1981 est., $43,420,000.)

Activities	Objective	Notes
1. Study gamete transport in mammalian reproductive tracts.	Increase basic knowledge of gamete transport for better understanding of fertility and infertility.	
2. Conduct basic studies in reproductive genetics.	Enhance fundamental science base for understanding chromosomal disorders.	Coordinate with the NICHD Work Group on Genetics and Teratology.
3. Support animal studies on in vitro fertilization, embryo transfer, and embryonic and endometrial synchrony for implantation.	Develop a program announcement for studies in nonhuman primates.	Basic knowledge on fertilization and implantation in mammals is needed to help alleviate disorders of infertility.
4. Develop new technologies such as hybridomas and recombinant DNA.	Increase fundamental science base on reproduction.	Cordinate with the NIADDK.
	Plan a research workshop on gene regulation to identify broad areas of research.	The production of single monoclonal antibodies serves as a potent new biotechnology in reproduction.
5. Support basic research on the biosynthesis, secretion, and action of reproductive hormones.	Increase fundamental science base to understand the endocrinology of reproduction.	Cosponsor, in the summer of 1982, the Ovarian Workshop with Society for Study of Reproduction.
6. Conduct further studies on fundamental reproductive neuroendocrinology.	Develop basic knowledge on the control of reproductive processes by the brain and other components of the nervous system.	New knowledge in this area is essential to understanding fertility and infertility.

Human Fertility. Program goal: To develop new knowledge that can be applied to alleviate and/or cure human infertility. (Fiscal Year 1981 est., $1,798,000.)

Activities	Objective	Notes
7. Support fundamental research on gonadotropin-releasing hormone and its analogs; study new methods for detection of human chorionic gonadotropin.	Develop new understandings on safer, more efficacious means of ovulation induction and prediction. Develop methods for early detection of ectopic pregnancy.	Coordinate internally with research program on Contraceptive Development.
8. Conduct basic studies on tubal physiology, gamete transport, and cervical mucus.	Provide a scientific basis for correction of fallopian tubal abnormalities and defects and for self-evaluation of cervical mucus.	Consult with American Fertility Society and with natural family planning groups.
9. Study the mechanisms for stimulating sperm production and develop better methods to evaluate sperm quality.	Identify new approaches to treatment of male infertility.	Utilize findings and recommendations of the NICHD Testes Workshop.
10. Study the suppression of testosterone production in women.	Develop methods to alleviate infertility in women due to hypersecretion of testosterone.	Consult with the Society for Gynecological Investigation.
11. Determine mechanisms of follicular growth and ovulation.	Increase fundamental science base on ovarian physiology.	Cosponsor, in the summer of 1982, the Ovarian Workshop with the Society for Study of Reproduction.

Reproductive Diseases and Disorders. Program goal: To alleviate or cure human reproductive diseases or disorders. (Fiscal Year 1981 est., $1,261,000.)

Activities	Objective	Notes
12. Elucidate the role of endogenous opioids in reproduction.	Develop program announcement.	Coordinate with the NINCDS.
13. Study catecholamines as neurotransmitters in reproduction.	Develop program announcement.	Coordinate with the NINCDS.

Reproductive Diseases and Disorders--Continued

Activities	Objectives	Notes
		Further studies of the role of catecholamines in modulating hypothalamic hormone secretions, and the role of dopamine in acting as a prolactin-inhibiting factor, are of urgent importance.
14. Study female reproductive dysfunction including dysmenorrhea, endometriosis, exercise-induced amenorrhea, and immune or autoimmune disease.	Develop program announcement; encourage studies on the etiology and amelioration of reproductive dysfunction in women.	Coordinate with the American College of Obstetricians and Gynecologists.
	Develop new knowledge on the role of nutrition in menstrual dysfunction.	Coordinate internally with research program on Nutrition.
15. Conduct research on reproductive toxicology and the environment.	Convene experts in field to assist in identifying new research questions.	Broad emphasis on reproductive toxicology deserves considerable attention in view of risk for both male and female. Coordinate with NIEHS and NIOSH on possible conference or research workshop.
16. Investigate male gonadal dysfunction.	Increase studies on andrology including factors affecting and controlling male reproductive processes and plan a workshop in reproductive disease.	

Fertility Regulation. Program goal: To identify and develop new leads for basic research for less hazardous and more effective methods of fertility regulation. (Fiscal Year 1981 est., $789,000.)

Activities	Objective	Notes
17. Support fundamental work on gonadotropin releasing hormone analogs and on endogenous putative peptides.	Increase clinical work and studies on subhuman primates.	Coordinate internally with research program on Contraceptive Development, and consult with the Society for the Study of Reproduction and with the Endocrine Society.
18. Develop new understandings on Sertoli cell-germ cell interaction and sperm maturation.	Clarify the regional difference in epididymal function in sperm maturation; and clarify sperm motility acquisition.	Consult with the American Society of Andrology.
19. Study immunocontraception using antigens of sperm and zona pellucida.	Expand utilization of monoclonal antibody techniques.	Consult with a panel of immunologists.
20. Study the regulation of gonadal membrane receptors for reproductive peptide hormones.	Increase clinical work and studies on subhuman primates.	Consult with the Endocrine Society.
21. Study the regulatory mechanism of oocyte maturation.	Clarify factors involved in the oocyte maturation and their control mechanisms.	

Evidence of Program Performance

In October 1979, NICHD received approval of funds for the evaluation of its 10 program-emphasis areas of research. The program objectives and activities as stated above were developed for the NICHD program emphasis area "Fertility and Infertility," as part of a major evaluation of the Institute's research activity.

Study Groups, consisting of one or more outstanding biomedical or behavioral scientists from the Nation's research community and members of the Institute's extramural and intramural staff, were appointed for each of the 10 NICHD areas. The Study Groups were formally charged in February 1980 with responsibility to evaluate the state of the science, identify areas of promise, and recommend directions for future research. Beginning in July 1980, the Steering Committee conducted an extensive examination involving scientific and policy review of each of the Study Group reports.

The reports have been used by the Institute as primary sources to evaluate its program activity and develop plans for future research. Each program area will be reviewed and updated annually as part of the NICHD planning and evaluation process. By this means, areas not emphasized adequately can be addressed, the guidance of other experts can be sought, and changes in the state of the science and changes in health issues can be accommodated. On a continuing basis, the Institute will be able to monitor its research progress and address the full breadth of research needs with each program area.

Following are short summaries of some recent findings and accomplishments of the program on Fertility and Infertility.

Mechanisms of Steroid Hormone Action. An in vitro cell culture system for chick oviduct tissues has been developed.(1) This technological advance is of significant interest to those researchers working on the mechanisms of steroid and peptide hormone action. Steroid hormone regulation of gene expression is directly implicated in many health-related problems involving reproductive tissues.

Purification of Steroid Receptors. Researchers have succeeded in stabilizing the steroid receptors by molybdate.(2) This finding enables precise physical characterization of androgen as well as progesterone receptors to be made for the first time. Previously much difficulty was encountered in clarifying the mechanism of action of these steroid hormones due to the unstable nature of the receptors for progesterone and androgen.

Monoclonal Antibodies and Sperm Maturation. Significant progress has been made in identifying and characterizing specific surface components of sperm in order to determine their role in reproduction.(3) This research has provided the first solid evidence that individual antigenic determinants are restricted to specific areas of the sperm surface and has demonstrated for the first time that sperm surface components produced by other cells in the reproductive tract become applied to and associated with specific topographically restricted areas of the sperm surface.

Chemically Defined Medium for Sperm Motility Research. The study of sperm function in vitro has been furthered by the development and use of a new chemically defined medium.(4) A synthetic polymer, polyvinyl alcohol, recently was found to have very useful properties for this purpose. Use of this polymer in place of serum protein permits separation of sperm motility from fertilizability.

Mechanism of Gossypol Inhibition of Male Fertility. The mechanism of the effect on fertility of gossypol, a nonsteroidal compound that inhibits sperm production in animals and humans, has been further clarified.(5) Researchers have demonstrated, for the first time, that gossypol interferes with testosterone production by the Leydig cells of the testis. Serum testosterone and luteinizing hormone (LH) levels were significantly reduced following the administration of gossypol to rats at concentrations which inhibited fertility without an apparent loss of libido. Sperm in the resulting ejaculates were reduced in number and rendered immotile.

Regulation of Gonadotropin Secretion. Substantial progress has been made concerning hypothalamic control of gonadotropin secretion in the rhesus monkey.(6) A model for neuroendocrine control of the menstrual cycle in this species has been developed that can probably be extrapolated in large degree to the human female.

Brain Peptides and Gonadotropin Secretion. Studies in opiate research have enhanced our understanding of neuroendocrine control of pituitary function.(7) This research provides indirect evidence that endogenous opiates may play an important role in control of gonadotropin-releasing hormone (GnRH) secretion during the menstrual cycle.

Mechanism of GnRH Action. Research has further elucidated the mechanism of action of gonadotropin-releasing hormone.(8) The findings have made it possible to postulate that GnRH action may be divided into three sequential steps, namely: interaction of GnRH with a specific plasma membrane recepter; mobilization of ionic calcium; and expulsion of the contents of the gonadotropin secretory granule into the extracellular space.

Endocrine Response to Exercise. Significant new observations have been made regarding endocrine responses to exercise.(9) It was found that the increased secretion of hormones with potentially anti-reproductive action during exercise may contribute to hypothalamic amenorrhea in women athletes. While height/weight disparity may be a critical factor affecting optimal reproductive function, preliminary studies indicate that alternations in hypothalamic control of gonadotropin release, independently of body composition, may also be operant in the development of "athletic amenorrhea."

Secretion of Progesterone by Corpus Luteum. Studies have provided a more complete understanding of the corpus luteum.(10) The findings suggest that the difference in responsiveness between large and small luteal cells to luteinizing hormone (LH) is likely due to differences in the number of receptors for LH associated with the different cell types. Since the initial step in the complex process of progesterone synthesis and secretion is the binding of LH to its receptor, this research may lead to new mechanisms susceptible to contraceptive regulation.

Blood Lipoproteins in Ovarian Function. Research has clarified the mechansims by which ovarian cells acquire cholesterol from the circulating lipoprotein pool as a substrate for steroidogenesis.(11) These studies increase our understanding of the control of steroidogenesis and also provide new approaches for investigating the cause of defective corpus luteum function.

Oviductal Function and Ovulation. Findings from research in a rabbit model indicate that alternations of oviductal structure and function influence ipsilateral ovulatory function.(12) Removal of the fimbriae only on one side resulted in a significant decrease in the numbers of ovulations in the ipsilateral ovary. Such studies of oviductal function in relation to ovulatory function may lead to a better understanding of persistent infertility following restorative oviductal surgery.

Documentation

References:

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(2) Ryan, Robert J. P50-HD-09140 Model of Action of Reproductive Hormones.
Bardin, Clyde W. P60-HD-13541 Specialized Population Research Center.

(3) Eddy, Edward M. R01-HD-14054 Analysis of Sperm Surface Components.

(4) Bavister, Barry D. R01-HD-14235 Physiological and Biochemical Study of Sperm Motility.

(5) Friend, Daniel S. R01-HD-10445 Reversible Infertility and Sperm Membrane Structure.
Dym, Martin R01-HD-06969 The Role of the Sertoli Cells in Spermatogenesis.

(6) Knobil, Ernst R01-HD-103968 Studies on Reproductive Physiology in the Macaque.

(7) Yen, Samuel S. P01-HD-12303 Control of the Hypothalamic-Hypophyseal-Ovarian System.
Ferin, Michel J. R01-HD-10873 The Hypophysis and Reproduction in Rhesus Monkeys.

(8) Conn, Paul M. R01-HD-13220 Gonadotropin-Releasing Hormone Action: Role of CA2+.

(9) Yen, Samuel S. P01-HD-12303 Control of the Hypothalamic-Hypophyseal Ovarian System.

(10) Niswender, Gordon D. R01-HD-11590 Regulation of LH Receptors and Progesterone Secretion.
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(11) Strauss, Jermone F. R01-HD-12314 The Role of Blood Lipoproteins in Ovarian Function.

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Director's Overview

The mission of the National Institute of Dental Research (NIDR) is "to conduct, assist and foster researches, investigations, experiments and studies related to the cause, prevention, and methods of diagnosis and treatment of dental diseases and conditions." These dental diseases and conditions include dental caries, periodontal diseases, cleft lip and palate, malocclusions, oral cancer, soft tissue diseases and disorders, and injuries to the head and/or facial region.

Even though major advances have been made in prevention, dental caries is still the most common oral disease in the United States and is the primary cause of tooth loss through young adulthood. By age 35, the average American has lost five teeth as a result of dental caries and eleven more teeth have been attacked by this disease. Periodontal diseases effect nearly 75 percent of the adult population in this country and are the most common cause of tooth loss in people over 35 years of age. Nearly 6,000 babies are born each year with some form of cleft lip or palate, or both, which results in nearly 300,000 persons with these conditions in the United States. Over one-half of all children are estimated to have a malocclusion. Approximately 7,000 American lives are lost each year as a result of oral cancer, and a large segment of our population (approximately 70 percent) experience recurrent oral ulcerative disturbances. Approximately 10.5 million Americans sustain traumatic injuries requiring medical attention to the head and oral-facial region each year.

The results of neglect commonly are pain, loss of teeth, and destruction of the supporting structures of the teeth which can lead to disfigurement, impaired speech and chewing ability, as well as difficulties in social interactions. The National Center for Health Statistics (NCHS) has estimated that two-thirds of the population in the United States needed some kind of dental treatment. These health needs, the Nation's dental bill of $14.7 billion in 1980, and the 5.6 million days lost from work in 1976, reflect the enormous economic and social burden that these oral problems precipitate.

The NIDR research program strategy that has been developed to deal with these health problems includes the support and conduct of research on dental caries, periodontal diseases, craniofacial anomalies, soft tissue diseases and conditions, nutritional factors associated with oral health, restorative treatment materials, and pain mechanisms and control measures, as well as behavioral and social factors related to oral health and its promotion. Since dental caries and periodontal diseases are the two most prevalent oral diseases in our population, the research directed towards them receives high priority in this Institute.

The National Caries Program (NCP) plans and coordinates the development of techniques to prevent dental caries. Its research is in four strategy areas: combating the microbial agent, enhancing tooth resistance, improving diet and nutrition, and improving delivery systems. In pursuing the area of combating the microbial agent, the Program is investigating the pathophysiology of oral microorganisms, the etiology and epidemiology of dental caries, the identification and development of antimicrobial and antiplaque agents and development of an anticaries vaccine. Mechanisms of action of fluorides, improved means of fluoride delivery and adhesive tooth sealants are being investigated in efforts to increase tooth resistance. Research aimed at modifying the diet include development of noncariogenic sweeteners, diet supplementation and modification, and dietary trace elements. Studies on cost/benefit analysis of caries preventive procedures, motivation and acceptance of such procedures by individuals, communities, and health care providers, and the development of a methodology for early caries detection are included in the strategy to improve delivery and acceptance of caries preventive methods.

The goal of the Periodontal Disease Program is to develop preventive measures that can be initiated at an early age and continued throughout life to maintain natural teeth and supportive structures. To achieve this goal an objective of this Program includes the development of a better understanding of basic periodontal disease processes. In this regard investigations are being directed towards elucidating the host mechanisms involved in periodontal diseases, and identifying the microorganisms which are potentially pathogenic and the microbial mechanisms involved in the development of these diseases. The other Program objectives include the development of improved preventive, diagnostic, and treatment methods.

The Craniofacial Anomalies Program pursues research in the areas of congenital anomalies, dentofacial malrelations, and acquired defects. The established goals address the need to prevent the occurrence and reduce the severity of these entities. The research objectives generally fall into investigations of epidemiology, basic science, prevention and diagnosis and treatment.

The long range goal of the Restorative Materials Program is the improvement of oral health through research on dental biomaterials and associated technology. Efforts in this Program involve the development of new and the improvement of existing biomaterials, clinical procedures and methods of evaluation. Specifically the Program supports research in the areas of intracoronal restorative materials, prosthetic and maxillofacial prosthetic materials, endodontics, tooth implants, transplants and replants, and dental technology.

Studies on soft tissue diseases, such as recurrent aphthous ulcers, herpes viruses, and oral cancer, and on mineralization, salivary secretions, and nutrition are supported by the Soft Tissue Stomatology and Nutrition

Program. Research is directed towards understanding the normal oral structures as well as the nature and causes of related diseases in these areas and towards investigations of methods to prevent, diagnose, and treat the diseases.

The Pain Control and Behavioral Studies Program comprises two components. Research on pain and pain control primarily focuses on oral-facial pain and sensory-motor dysfunction: their etiology, epidemiology, prevention, diagnosis, and treatment. The identification of the neurobiological and pathophysiological bases are being pursued. Behavioral research includes the determination of how behavioral, social, cultural, and economic factors influence oral health and oral diseases or conditions, as well as the potential of these factors for enhancing health promotion and disease prevention. This latter area constitutes an increasingly important new activity for the NIDR.

Refinement of the NIDR program strategies has occurred in recent years through formal evaluation and planning efforts. To date, the Institute has completed evaluations of its Periodontal Diseases Program and the National Caries Program, and currently is evaluating the Craniofacial Anomalies Program. Evaluations for the NIDR's remaining programs are planned for the next several years.

In FY 1980, goals and objectives were reviewed and/or developed for the six NIDR categorical programs and for the Dental Research Institutes and Centers. These goals and objectives, which address the component parts of the broad mission of NIDR, not only provide a basis for evaluation purposes but also find application in current planning efforts. In FY 1981, the development of a Five Year Long Range Research Plan was initiated. This Plan will provide a thorough analysis of progress to date in dental research, a summary of research needs, and recommendations for program priorities. It is anticipated that the document will be useful not only in the NIDR planning efforts, but also in serving as a reference work for the outside research community and the various groups that support research.

FY 1981: Research Holding Great Promise for Progress and/or Major Advances and Recent Accomplishments

Caries

- Prospects for a vaccine against dental caries continue to improve. A protein that is crucial to the virulence of the cariogenic microorganism, S. mutans, has been isolated. Animals immunized with this protein have been found to have increased resistance to dental caries. In addition, a small scale human pilot study has shown a marked increase in antibody production after oral administration of killed S. mutans.

- Substantial progress has been made in developing an appliance for long-term, continuous release of agents at therapeutic levels in the mouth. Tests of prototypes of this device in adults suggest that caries-preventive levels of fluoride can be maintained in the mouth for extended periods of time. This device offers potential of being highly effective in preventing caries in particularly susceptible individuals.

Periodontal Disease

- Progress has been made in developing laboratory diagnostic tests which may provide objective measures of specific periodontal disease activity. The assays involve the measurement of prostaglandin (a mediator of bone resorption) in gingival pocket fluid and the measurement of serum antibodies to a bacterium associated with periodontal disease. In addition, progress has been made in developing radiographic techniques for detecting minute changes in the quality of supporting bone. Such tests may provide improved means of monitoring the efficacy of periodontal therapy.

- Continuing progress is being made in the area of host parasite relationship in periodontal disease. In these studies, organisms suspected of causing some forms of disease are being identified and the mechanisms by which they cause tissue destruction are being elucidated. Current studies indicate that specific bacterial substances may cause damage, or they may evoke host immune responses that in turn are destructive.

Craniofacial Anomalies

- Studies on the role of phenytoin (dilantin) in the cause of cleft lip and palate have shown that similar teratogenic effects occur in man and in certain strains of mice. In addition, the drug can cause acute central nervous system (CNS) toxicity in both species. The increased susceptibility of some humans to teratogens such as phenytoin and alcohol may be associated with certain cell surface markers in the mother, which suggests a genetic predisposition. Further studies in this area are expected to yield important knowledge relating to the mechanism action of phenytoin and other teratogens.

- Promising areas of research for FY 1981 include the factors responsible for cell proliferation, migration, and differentiation. Since the neural crest makes major contributions to the development of the craniofacial region, these cells and the extracellular matrix components with which they interact will be the focus of study. Among the extracellular matrix macromolecules, hyaluronate appears to play an important role in facilitating neural crest migration and perhaps in regulating differentiation. In wound healing, on the other hand, different substances appear to regulate cell activity, and continuing studies of the extracellular matrices are expected to yield important insights on the control of normal and abnormal craniofacial development as well as of tissue repair processes.

Restorative Materials

- Investigators have developed a laboratory device to analyze and measure the wear of composite and silver amalgam filling materials. This device should be helpful in testing the strength of new experimental materials.

- A project to develop a diagnostic X-ray system which will enable scientists to systematically observe and record the progress of common dental pathoses, such as periodontal disease and caries, has been initiated. The system envisioned will employ a dental X-ray source detector and an image processing computer, which will make it possible to standardize the radiographs so that direct comparisons can be made of films taken at different times in the same individual.

- A magnetic aiming device for dental X-ray machines, which accurately positions the cone over the film in the patient's mouth without requiring uncomfortable hardware, is being developed. The device will permit a substantial reduction in field size and radiation dose to normal tissues. This could be a major development in the field of dental radiology.

Soft Tissue Stomatology and Nutrition

- Fever blisters and certain infections of the skin and eyes are caused by the herpes simplex virus. Researchers have isolated a protein from the virus surface coat and they have produced antibodies to this protein. When mice were injected with these antigens, they became immune to lethal doses of the virus. Work is continuing toward human application of this research.

- Chemotherapeutic agents used against cancer frequently cause severe side effects on oral tissues. Studies have shown that small changes in saliva composition and volume are seen early in chemotherapy before more serious side effects occur. These early warning signs in the saliva may allow clinicians to adjust dosage so as to maximize benefit while minimizing damage to other tissues.

- Work on the regulation of calcification indicates that parathyroid hormone increases the permeability of bone cell membranes to calcium, which acts as an intracellular mediator of hormone action. Studies of this type will lead to a better understanding of bone metabolism and tooth development and may provide a more rational basis for treatment of hard tissue diseases.

- An extracellular protein has been identified which binds strongly to both collagen and calcium. The protein, named osteonectin, appears to be unique to bone. Further studies are directed toward defining the role of osteonectin in mineralization.

Pain Control and Behavioral Studies

- Studies of factors influencing post-operative dental pain indicate that the relief obtained by placebo administration is mediated by natural opium-like substances in the brain, and that this placebo effect is more pronounced in patients with severe pain than in those with mild pain. These studies contribute to our information base on the neurobiological mechanisms of pain control and, hopefully, will contribute to the development of improved methods for controlling pain.

- Progress has been made in developing a means by which investigators can measure fear of dental treatment and to develop techniques to reduce it. The next step toward practical application is to evaluate these techniques in routine dental practice settings.

FY 1982 Program Changes

Major Activities to be Initiated

Periodontal Diseases

- Investigations to develop new and improved diagnostic methods.*

Restorative Materials

- New studies on base-metal alloys to substitute for gold.

Major Activities to be Maintained or Expanded

Caries

- Clinical trials of fluoride-based agents, such as fluoride supplements and fluoride-containing mouth rinses,* will be maintained.

Periodontal Diseases

- Investigations on the identification and characterization of gingival bacterial flora* will be maintained.
- Studies of the host response to plaque factors--including the immunologic mechanisms involved in inflammation, tissue repair, and tissue destruction*--will be maintained.
- Studies of the prevention and therapy of periodontal diseases, including projects to develop antimicrobial agents and slow-release delivery systems,* will be maintained.

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* Throughout the sections on FY 1982 and 1983 program changes, the asterisks(*) indicate scientific areas recommended for emphasis by the formal evaluations of the Periodontal Disease Research Activity and the National Caries Program, respectively. (References: Evaluation of the NIDR Periodontal Disease Research Activity, April 1976; Evaluation of the National Institute of Dental Research National Caries Program, Vols. 1, 2, 3, November 1979.)

- Investigations to define the relationship between periodontal diseases and diabetes, dietary deficiencies, and immune deficiencies* will be maintained.

- A clinical trial of periodontal therapeutic methods involving intensive oral hygiene procedures* will be maintained.

Craniofacial Anomalies

- Studies on the cellular and molecular basis of tissue form and function, such as are regulated by fibronectin and laminin, will be maintained.

- Development of animal models for the study of the pathogenesis of cleft lip/palate will be maintained.

- Investigations to test the efficacy and stability of orthognathic procedures for correction of severe malocclusions and disfigurements will be maintained.

- Studies of acquired disfigurement with emphasis on wound healing will be maintained.

- Studies of the mechanism of action of teratogens will be maintained.

Restorative Materials

- Laboratory and clinical research on tooth implants will be expanded.

- Laboratory and clinical studies on endodontic materials and treatment methods will be expanded.

- Laboratory and clinical research on composite filling materials will be maintained.

- Development of improved means for providing reproducible geometry of radiographic images will be maintained.

Soft Tissue Stomatology and Nutrition

- Research on oral viral diseases--including how viruses can increase a cell's susceptibility to specific bacterial infections, improvements in the application of antiviral agents to the sites of viral infections, and development of antiviral vaccines--will be expanded.

- Nutrition research, emphasizing the role of specific nutrients and potential methods of using diet and nutritional knowledge in the prevention and management of specific oral diseases, will be maintained.

- Oral ulcerative disease research--including studies to determine the etiology, pathogenesis, and treatment of recurrent aphthous stomatitis--will be maintained.

- Salivary secretion research, stressing the identification and characterization of constituents of saliva and their physiologic function(s), will be maintained.

- Studies exploring the biologic effects of fluoride will be maintained.

Major Activities to be Cut Back, Eliminated, or Not Started

Caries

- Planned clinical trials of slow-release devices for fluoride* will be cut back.

- Investigations to identify new noncarcinogenic sweeteners and characterize bulking agents* will not be started.

- Demonstration studies of fluoride-containing preventive agents, such as mouth-rinse programs in areas with fluoridated water supplies and supplements for high school children, will not be started.

- Investigations on the development of an anti-caries vaccine, with emphasis on obtaining more highly purified immunogens, will be cut back.

Craniofacial Anomalies

- Postnatal developmental studies will be cut back.

- Clinical research of cleft lip/palate will be cut back.

- Dentofacial malrelations investigations will be cut back.

Restorative Materials

- Laboratory and clinical silver amalgam research will be cut back.

Soft Tissue Stomatology and Nutrition

- Mineral metabolism studies, stressing invertebrate model systems, will be cut back.

- Epidemiological studies of oral cancer will be cut back.

Pain Control and Behavioral Studies

- Multidisciplinary oral-facial pain research--a combination of clinical, physiological, and psychological studies--will be cut back.

- Sociobehavioral research on fear and anxiety associated with dental treatment will be cut back.

- New studies dealing with sociobehavioral factors influencing oral health promotion will not be started.

Dental Research Institutes and Centers

- Planned expansion of clinical research capabilities will not be implemented.

Intramural

- The oral pharyngeal physiology program will be terminated.
- Further development of new radiographic diagnostic methodology will not be initiated.
- Studies on oral papillomas will be cut back.
- Equipment needs will not be met.

FY 1983 Program Changes

Major Activities to be Initiated

Caries

- Investigations to evaluate bulking agents for use with noncariogenic high intensity sweeteners.*

Periodontal Diseases

- Clinical trials of new diagnostic methods.*

Major Activities to be Maintained or Expanded

Caries

- Clinical trials of fluoride-based agents, such as fluoride supplements and fluoride-containing mouth rinses,* will be maintained.
- Clinical trials of fluoride slow-release devices* will be expanded.
- Anticaries vaccine development, with focus on the immunization and safety studies, will be expanded.
- Identification of factors contributing to the cariogenicity of foods* will be expanded.

Periodontal Diseases

- A clinical trial of periodontal therapeutic methods involving intensive oral hygiene procedures* will be maintained.

- Investigations on the identification and characterization of gingival bacterial flora* will be maintained.

- Studies of the host response to plaque factors--including the immunologic mechanisms involved in inflammation, tissue repair, and tissue destruction--will be maintained.

- Studies on the prevention and therapy of periodontal diseases, including projects to develop antimicrobial agents and slow-release delivery systems,* will be maintained.

- Investigations to define the relationship between periodontal diseases and diabetes, dietary deficiencies, and immune deficiencies* will be maintained.

Craniofacial Anomalies

- Developmental biology investigations, with emphasis on the extracellular matrix and differentiation and control of migration of neural crest cells, will be expanded.

- Studies of wound healing, with reference to trauma and oral cancer causation, will be expanded.

Restorative Materials

- Investigations of base-metal alloys as substitutes for gold will be expanded.

Soft Tissue Stomatology and Nutrition

- Development and testing of an antiherpes virus vaccine will be maintained.

- Mineral metabolism research will be maintained.

- Research on oral viral diseases, including how viruses can increase a cell's susceptibility to specific bacterial infections, and improvements in the application of antiviral agents to the sites of viral infections will be maintained.

- Nutrition research, emphasizing the role of specific nutrients and potential methods of using diet and nutritional knowledge in the prevention and management of specific oral disease, will be maintained.

- Oral ulcerative disease research--including studies to determine the etiology, pathogenesis, and treatment of recurrent aphthous stomatitis--will be maintained.

- Salivary secretion research, stressing the identification and characterization of constituents of saliva and their physiologic function(s), will be maintained.

- Studies emphasizing the biologic effects of fluoride will be maintained.

Pain Control and Behavioral Studies

- Multidisciplinary oral-facial pain research--a combination of clinical, physiological, and psychological studies--will be maintained.
- Social and behavioral studies of fear and anxiety associated with dental treatment will be maintained.
- Investigations of sociobehavioral factors influencing oral health promotion will be maintained.

Dental Research Institutes and Centers

- Research on immunology, microbiology, molecular biology, and mineralization that contributes to applied studies in caries, periodontal disease, and herpes labialis will be maintained.

Intramural

- Research concerned with the management of chronic pain will be maintained.
- Basic research concerned with diabetes mellitus, mineralization, attachment proteins, immune factors, chemotaxis, and teratology will be maintained.
- Development and testing of new dental radiographic diagnostic procedures will be maintained.
- Equipment needs will be met.

Training

- Clinical investigators will be trained for a wide variety of studies in dental research.

Potential Impact of Program Changes on Three-Year Period (1983-1985)

The research goals and objectives of the NIDR specify research on the etiology, pathogenesis, epidemiology, prevention, diagnosis, and treatment of oral diseases and conditions. The efforts are directed towards moving the science through the biomedical research spectrum from basic to applied research and implementing clinical investigations, clinical trials, and demonstration programs. The momentum of moving through this spectrum has been decreased as a result of FY 1982 and FY 1983 program changes.

A large number of the NIDR program changes involving reduction, cutback, elimination, or not-to-be-initiated project activity in FY 1982 involve clinical and applications research. The majority of these are supported through the contract mechanism, which is particularly suitable for epidemiologic research, clinical trials, and demonstration projects. This reduction in contract supported research resulted from the stabilization of science-base activities supported by research grants.

An example of the impact of these changes can be shown through viewing caries research activities. Significant advances for FY 1981 included further development of the caries vaccine and substantial progress in the development of a fluoride-containing slow-release device. In FY 1982, budget reductions necessitated cutbacks in these two areas. Although this research is planned for expansion in FY 1983, progress has been affected.

FY 1982 and FY 1983 program changes permit the maintenance of most of the research activities and the initiation of only a few new activities. Additional funds will be needed during the three-year planning period in order to initiate new and expand existing activities in all program categories. In caries research this would include the initiation of the development of intraoral slow-release delivery systems for antimicrobial and antiplaque agents, as well as the expansion of the anticaries vaccine development, and studies evaluating the replacement of cariogenic by noncariogenic oral flora. In studies of periodontal diseases, all research activities mentioned in FY 1983 program changes would be expanded. To advance knowledge of craniofacial anomalies, NIDR would initiate training programs in immunogenetics and molecular biology, studies on temporomandibular joint dysfunction in humans and animals, computer graphic analysis and simulation of craniofacial morphogenesis and treatment, and comprehensive long-term research on the major problems of individuals with acquired defects. Restorative materials activities would include expansion of research on tooth implants, endodontics, and metallic substitutes for gold. Studies of oral ulcerative diseases would be expanded, as would programs in nutrition research and training. New programs to study oral viral disease would be initiated. Studies to evaluate the effectiveness and side-effects of dental anesthesia, sedation, and multidisciplinary oral-facial pain research activities would be expanded. In the area of behavioral studies, institutional research training programs would be initiated to produce qualified investigators for oral health behavioral research and to conduct additional research on sociobehavioral concomitants of changes in dental-facial appearance. Major expansion of the intramural clinical research program and changes in basic research activity will require additional funds. These funds will support the expansion of the chronic pain program, clinical trials of periodontal treatment modalities, development of a herpes simplex vaccine, studies on oral premalignant and malignant lesions, as well as studies on the management of oral disease in medically compromised patients.

NIDR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Institute of Dental Research

DATE: JAN 30 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I was pleased to learn that the Institute has begun the task of developing a comprehensive five year research plan. Those Institutes who have developed similar plans have been served well by the effort. I would encourage you to address not only areas of emphasis and opportunity in your plan, but also a strategy for relating opportunities to resources available during periods of economic constraint. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

D S Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

The Institute is developing a comprehensive five-year research plan. A series of state-of-the-science papers will be compiled for each research area within NIDR: dental caries; periodontal diseases; soft tissue, stomatology and nutrition; craniofacial anomalies; restorative materials; and pain control and behavioral studies. The long-range plan will define areas of research emphasis and opportunity, point out resources needed to achieve progress in these areas, and propose a strategy for relating opportunities to resources available during periods of economic constraint.

Impact of Stabilization

- The total number of research project grants supported will remain relatively stable during the period 1981-83; however, the number of competing awards to be made in 1983 will drop substantially due to a pronounced irregular cycling problem.

- The number of research centers supported and the funds allocated to them will remain the same, although purchasing power will decrease because of inflation. The number of research career awards will decrease substantially in 1982.

- The number of R&D contracts to be awarded in 1982 will decrease by approximately 50 percent from 1980 levels, seriously limiting clinical studies and applications research.

- The Intramural Research Program will remain at about the same level of activity during the 1981-83 period.

- The support for clinical trials will be reduced. Research needs which will not be met within the projected funding levels are in the areas of establishing objective criteria for measuring periodontal diseases, behavioral research, research on bone, and further research in diabetes and diabetic dental complications, especially in initiating research in maturity onset diabetes.

Research Activities

Prevention. The development of vaccines for caries prevention and against oral herpes virus infections is progressing; however, additional funds will be necessary for the Institute to develop clinical trials and to underwrite part of the needed toxicology tests.

Clinical trials of intraoral devices which provide a slow release of fluorides, and of combined application of occlusal surface sealants, for pits and fissures, and topical fluorides, for smooth surfaces, are in progress.

A list of acceptable snack foods is in preparation for release to the public. Foods for inclusion on the list are being tested for cariogenicity. Television, radio, and print releases are planned.

Diagnosis. A computerized process for comparing minute changes in X-rays of periodontal patients has been developed. This allows the observation of new bone formation or bone destruction long before it can be observed by conventional methods, and could be used as a sensitive monitoring device for treatment.

Treatment. Large scale clinical trials are being planned for testing the efficacy of phase microscopic evaluation of bacterial activity in determining current activity of periodontal diseases and the progress of therapy. As part of the project, standard home care procedures will be compared with a regimen of intensified measures. The latter method involves self-administered flossing, irrigation, application of salts and oxygenating antiseptic combined with other treatments, such as the use of antibiotics. The patients included in these studies will have moderate disease states, where conventional treatment would not normally be started. An RFP (request for proposal) has already been issued.

Basic Science. Studies of chemotactic agents, such as fibronectin, are under way. Better understanding of mechanisms of "attachment" proteins could lead to the development of treatments for periodontal diseases which would induce the reattachment of tissue.

In order to better predict the effects of chemotherapy, methods for measurement of the flow and composition of saliva are being developed. Such measures will allow for the detection of changes in patients receiving chemotherapy which are not otherwise observable.

The NIDR is funding research on the causes and processes of pain, particularly research concerning endorphins. The NIDR is prepared to take a leading role in the planned pain control clinic in the new Ambulatory Care Research Facility.

Issues

Stabilization of the research project grants has restricted the funds available for contracts (which are uniquely suited to clinical trials and epidemiological studies) and for intramural research. In order to capitalize on the investment in, and productivity of, the science base, the Institute should be in a position to move the progress of these investments toward useful applications and technology testing. This is difficult within present budgetary restrictions.

NIDR

Action Item

Please explore and suggest possible approaches that could be considered in developing relationships with the private sector, particularly in the area of vaccine development, and be prepared to address this issue during the spring/fall review sessions.

Applications Research

Statement of Issue

Need for increased support for applied research activities.

Discussion of Issue

Stabilization of science-base activities, primarily the support of research grants, has precipitated a restricted budget for contracts and intramural research. The contracts mechanism is particularly suitable for epidemiologic research, clinical trials, and certain demonstration research involving the behavioral and social sciences. Considerable gaps in our knowledge exist concerning the quantity and distribution of oral diseases, health and conditions in the United States. Without epidemiologic research to attain this information, it is difficult not only to assess progress toward disease prevention and health promotion, but even to assess the impact of differential socioenvironmental factors on the incidence and prevalence of the oral health problems of this country.

Clinical trials of various preventive agents such as intraoral slow-release fluoride devices for the prevention of dental caries in high risk individuals, of new noncariogenic sweeteners, and toxicology testing of drugs with potential of caries prevention are essential to the provision of these services to the public. These, as well as studies to develop techniques to measure cariogenicity of foods, are examples of activities which require the use of the contract mechanism or directed research to be accomplished intramurally.

Alternatives and/or Suggested Position

In view of the investment in science-base projects, the NIDR will be in a position to move progress of the research towards useful applications and technology testing. A significant increase in the budget, which can be applied to contracts and intramural research, must be provided before the potential of the science-base can be fully realized.

PROGRAM PERFORMANCE SUMMARY

NATIONAL CARIES PROGRAM

Program Description

The National Caries Program (NCP), established in 1971, is a coordinated research and development entity whose overall objective is to develop methods to prevent dental caries and ultimately eliminate it as a public health problem in the United States. It is a unique program within the National Institute of Dental Research (NIDR), in that it is a targeted effort which coordinates intramural research, extramurally supported research, and collaborative research under one Associate Director. This organizational structure permits the achievement of the NCP's overall objective through the conduct and the support of research to identify, develop and test, and to promote public adoption of safe, highly acceptable, and cost-effective caries-preventive agents and techniques. The National Caries Program is the major focus for research on caries prevention in the world and is regularly visited by American and foreign dental scientists. In recognition of the NCP's accomplishments, the European Organization for Caries Research is holding its 1982 meeting for the first time in the United States.

Dental caries is the most common disease in children in the United States and other technically advanced countries. It is chronic, insidious, and leads eventually to expensive clinical repair or to tooth loss and other sequelae. By age 11, more than 75 percent of all children in the United States have experienced caries in their permanent dentition.(1) Caries is the primary cause of tooth loss through adulthood, and by age 35 the average American has lost 5 teeth and has 11 more attacked by caries.(1) Americans spend in excess of $6 billion each year to repair damage caused by the disease.(2) This approaches one half of the $13.7 billion spent for dental care in 1979.(3)

Dental caries is a transmissible, multifactorial disease whose etiology includes the interaction of three principal factors--a susceptible host (the teeth), a cariogenic microflora (the bacteria), and a suitable substrate (the diet). The bacteria colonize the surfaces of teeth and metabolize carbohydrates in foods to form acids. These acids, when generated near the tooth surface, result in the decalcification of the local enamel and/or cementum. Subsequent to a meal, neutrality at these sites is slowly reestablished and the damaged enamel to some extent recalcifies. In addition to the capacity to remineralize the enamel, the host has several defense mechanisms involving secretory antibodies, enzymes, and other salivary factors to limit microbial activity in the mouth. When eating is frequent, however, and when the fermentable carbohydrate (particularly sucrose) content of these meals, beverages, and snacks is high, the host defense mechanisms are overwhelmed, decalcification progresses, and irreversible cavitation occurs. Untreated, the cavity will progress and result in bacteria penetrating into the tooth pulp.

Several microorganisms, *Streptococcus mutans*, *Actinomyces viscosus* and *Lactobacillus casei*, are believed to be the major pathogens in human caries.

Of these, S. mutans has been most extensively studied because of its efficient use of simple sugars, ability to prosper in an acidic environment, ability to colonize on smooth surfaces and to form adhesive glucans from sucrose, and because of numerous other characteristics that associate it with the disease.

The strategies used to develop preventive methods are based upon attempts to (1) increase the resistance of the host (fluorides, occlusal sealants), (2) lower the numbers of microorganisms in contact with the tooth (plaque control) or combat the microorganisms through immunization, and (3) modify the substrate by providing noncariogenic foodstuffs and/or limiting intake of cariogenic products. The NIDR, and its progenitor laboratories at NIH, pioneered the research on the role of fluoride on the prevention of dental caries. Today the most effective caries preventive method for community use remains the achievement of optimal fluoride levels (ranging from 0.7 to 1.2 ppm depending upon mean daily temperatures) in the municipal water supplies. Children who have ingested this water from birth show a 50-65 percent reduction in dental caries experience when compared with children who have not benefited from this water.

While the optimal level of fluoride in the public water supplies was being established in many American cities in the 1950s and '60s, dental scientists (largely supported by NIDR) were probing the etiology of caries to identify ways to eliminate the caries which develop even in the presence of fluoride and to identify preventive methods for localities that could not achieve optimum levels of fluoride in water supplies. By the mid-1960s, some of the major questions of caries etiology had been deciphered (it was a transmissible bacterial disease, it required frequent consumption of simple sugars in the diet, etc.) and many highly effective ways to control caries in laboratory models had been identified.

In 1967, in response to a Presidential request for information on NIH programs, the Director, NIDR, and the Planning Committee of the National Advisory Dental Research Council, reviewed the above findings and agreed that a more structured attack on caries was needed. As a result, an Institute task force was formed to coordinate caries research and, during the next 18 months, a program of activities was laid out and staff roles in it defined. In 1969, in response to a Congressional request for further information, the Institute submitted a review of caries and again described the potential for elimination of this disease. The President subsequently identified caries research as a health initiative and provided it a line item budget of $5 million in FY 1971. To marshal Institute capabilities in support of this initiative, the Director, NIDR, requested an organizational change, bringing together all Institute components already involved in caries research in a National Caries Program. This change was carried out in late 1971.

Through bringing the Institute intramural and extramural caries activities together, adding to it a clinical trials group from the Division of Dental Health, Bureau of Health Manpower Education, and forming a staff to administer contracts, the NCP was structured so that it could plan and coordinate activities across the spectrum of caries research and development. Of the innumerable administrative and scientific events occurring each year, a few noteworthy ones are listed below. Early in 1972 Dr. James Carlos was appointed Associate Director for the NCP, and an Advisory Committee was formed. In 1973 Dr. William Bowen, a renowned British cariologist, was appointed as visiting scientist to coordinate the laboratory activities. In 1974 discussions were initiated with pharmaceutical firms that led to the development of a program to screen candidate drugs as potential anticaries agents. Also in 1974 the NCP established its laboratory in the Auburn Building and a primate colony in Vienna, Va., for research on caries etiology and prevention; commenced a major survey among dentists that revealed enthusiasm towards caries prevention; and initiated a tailored program to train scientists in caries research.

In 1975 the Program undertook a national demonstration of school-based fluoride mouth-rinsing to promote use of this caries-preventive technique and finished a multiyear assessment of adhesive sealants. The years 1976 and 1977 were a period of consolidation marked by the presentation of five workshops on different aspects of caries etiology and prevention; formalization of a planning office in the NCP; completion of the first stage of research on planning methodologies; and establishment of collaborative projects with foreign scientists visiting the NCP laboratories. In 1978 the NCP laboratories were moved to the Park Building in Rockville, Md., and the contracted evaluation of the NCP commenced. In 1979 and 1980, the results of the demonstration of school-based fluoride mouth-rinsing were published; a program was implemented to develop capability to systematically evaluate cariogenicity of foods; a survey was implemented to measure caries prevalence in the U.S. school population; major advances were reported in developing intraoral devices for providing fluoride to individuals at high risk to caries; and major advances were reported in techniques for delivery of caries vaccines. Finally, the current year is marked by the availability of results from the national survey of caries prevalence.

The staffing and funding of the NCP have been quite consistent for the years 1978-82. The current 50-member staff consists of 25 intramural scientists, biometricians, contract project officers, health scientist administrators and health educators, and 25 technical and clerical support staff. Since 1978 the staff has increased by only four individuals. The NCP's funding for the same five years is presented in the following table by mechanism, number of projects, and thousands of dollars:

National Caries Program, 1978-82 Est.
(Dollars in Thousands)

	1978		1979		1980		1981 est.		Pres. bud. 1982 est.	
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
Research projects	91	$5,221	79	$5,746	82	$6,002	77	$6,281	79	7,319
Other research	3	77	5	155	5	155	4	155	6	254
Training	11	403	8	257	20	423	21	325	23	426
Total	105	$5,701	92	$6,158	107	$6,850	102	$6,761	108	$7,999
Contracts & inter-agency agreement	42	3,213	35	2,713	24	2,346	21	2,124	10	924
Direct operations		1,285		1,408		1,401		1,445		1,494
Intramural		846		931		1,085		1,096		1,100
Total		$11,045		$11,210		$11,412		$11,426		$11,517

The National Caries Program encompasses the Office of the Associate Director which plans and directs the Program's research and development activities and assures maximum utilization of resources. This Office includes the Associate Director, an Assistant to the Associate Director, a Chief of the Planning Unit and Deputy Associate Director, and a Public Health Educator. The Associate Director coordinates intramural, extramural, and collaborative staff through two branches--the Caries Prevention and Research Branch and the Caries Research Grants and Contracts Branch. The former Branch is organized into four sections, which include: (1) an Etiology Section, responsible for clarifying the etiology of caries to uncover new approaches to preventing the disease or to improving existing approaches to prevention; (2) a Preventive Methods Development Section, charged with assessing the feasibility of using the approaches identified at the etiologic level and charged with preclinical development and testing of agents; (3) a Community Programs Section, responsible for clinical and field testing of techniques established by preclinical research, and (4) a Biometry Section, which provides biometrical support and statistical interpretation of data arising from laboratory, clinical, and field studies. The Caries Research Grants and Contracts Branch is structured so that its staff can service the needs of the grantee community with publication of statements of program interests and RFAs (requests for applications) as well as implementing contracted activities needed by the Program.

The NCP's structure is designed to facilitate the translation of basic research findings into tested agents accepted by the public. The current development of a fluoride slow-release device is an example of the way in which staff of these branches and their respective sections collaborate. In 1973, the staff of the Etiology Section established that very small amounts of fluoride in the mouths of rats were protective against caries if present continuously. The possibility of maintaining these levels for long periods of time was explored through the contract mechanism and directly by staff of the Preventive Methods Development Section in the period 1974-78. Several prototype, intraoral slow-release devices were developed, and by 1979 these were tested in animals. With FDA approval, short-term clinical trials followed in 1980, and the Community Programs Section currrently is preparing to administer a longer-term clinical trial. If these trials and subsequent field studies of the acceptance of the device continue to show high promise, then the Program will undertake promoting the utilization of these devices initially in the populations at high risk to caries, for which they seem most appropriate, and then as experience warrants in more general applications.

Program Objectives and Activities

As has been stated, the NCP's overall objective is to develop methods to prevent caries and to ultimately eliminate dental caries as a public health problem in the United States. Within that overall objective there are four major research strategies, each being further defined at two levels: strategy components and component objectives. Strategy components are approaches to achieving the strategy (e.g., immunization is one way of combating the microorganism) and component objectives are major research objectives in the sequence of steps involved in developing the strategy component (e.g., "develop capability to measure specific salivary immunoglobulins" is an objective in the strategy component "immunization"). These strategies and their major components include:

- Combat the microorganism: Antimicrobial and antiplaque agents; Immunization.
- Increase tooth resistance: Fluoride-based techniques; Adhesive sealants.
- Decrease the cariogenic potential of the diet: Noncariogenic sweeteners.
- Improve delivery and acceptance of caries preventive methods.

Other important strategy components include investigating the disease through physiological, etiological, and epidemiological studies and developing Program effectiveness through improvements in research methods, planning, and research manpower.

Progress in developing each of the strategy components is measured by the component objectives that have been achieved. At the stage that techniques are transferred into public use, the progress of the NCP is measured directly in terms of changes in incidence of the disease and indirectly in terms of public participating in programs and utilization of preventive techniques.

The research, development, and transfer activities for each of the NCP's strategy activities have led to key research accomplishments. Specific accomplishments are enumerated in the report "Evaluation of the National Institute of Dental Research National Caries Program."(4) Brief highlights of past, ongoing, and projected activities are summarized in the following sections.

Antimicrobial and Antiplaque Agents

Commencing in the early '70s the Program established a collaborative screening program through which industry could obtain comparable, reliable information on merits of proprietary chemicals for caries prevention. Since then the NCP has worked with 38 companies, screened close to 300 potential agents in standardized *in vitro* tests and animal models, reported that about 15 agents had promise, and tested 5 agents in short-term clinical trials.

To overcome the problem of frequent application and to decrease the total amount of agent to which the body would be exposed, the NCP has developed an intraoral device for long-term release of therapeutic levels of agent close to the site of infection. The device, about the size of a child's aspirin tablet, is fastened with adhesive to a tooth surface and replaced periodically. The first model of the device, designed for slow-release of fluoride, has been demonstrated in animals to maintain the fluoride content of the saliva within the desired range for months. It is now being tested in short-term human trials. Its initial use will be in patients who are highly prone to caries (e.g., patients with decreased saliva flow due to irradiation of the head and neck region for cancer) or in patients who cannot maintain their own oral hygiene.

Immunization

The scientific view at the time the NCP was formed was that the possibility of immunizing against caries was doubtful because tooth enamel does not have a vascular system to transport antigens and antibodies. Additionally, it was doubtful from the public health point of view, for one would expect few persons to submit to transdermal vaccination (with its obvious element of risk) to prevent a non-life-threatening disease. Research in recent years, largely supported or conducted by NCP, has demonstrated successful immunization in animals, helped elucidate the mechanisms of secretory immunity, and showed that salivary immune responses can be obtained in man with immunogens provided orally. These advances make it appear possible to develop a vaccine against caries; however, the Program anticipates some years of work before an effective vaccine sufficiently safe for human use is demonstrated.

Fluoride-Based Programs

During the last few decades clinical investigators have tested a number of topical fluoride regimens to prevent caries. They have applied fluoride to the teeth in gels using custom-fitted mouth trays, and have incorporated it in tooth paste, chewable tablets, and in oral rinse solutions. In almost all cases they have found effectiveness against caries. Because of differences in these clinical trials in the way in which caries was measured and in other factors, the reported effectiveness of the agents cannot be compared with confidence. To overcome this problem the NCP is evaluating most of the noteworthy topical fluoride regimens under side-by-side conditions in carefully controlled clinical trials. In addition, the NCP staff is carrying out or supporting studies to establish whether certain regimens used in combination possibly have significantly higher effectiveness or to establish the optimal duration of school-based programs. Finally, the NCP's 17 demonstrations of caries prevention by community-run programs of fluoride mouth-rinsing in schools were concluded in FY 1980. Overall, approximately 80 thousand children participated in the demonstrations in grades K-6(8). Simultaneously the Program has been carrying out an educational effort to make communities throughout the Nation aware of these models and to assist them in establishing their own mouth-rinse (or other self-applied fluoride) program.

Adhesive Sealants

When the NCP was formed, several adhesive polymers were undergoing initial tests to assess whether they had value in sealing the pits and fissures of occlusal surfaces of posterior teeth. These sites, in which food debris lodge, are difficult to clean and highly susceptible to caries. Adhesive polymers were conceived to provide a possible solution to the problem, for they form an impermeable coating over these sites which prevents all caries as long as the coating remains in place. A number of factors, however, limit the public health usefulness of the procedure, of which the chief is the cost of the clinical time required to keep the surfaces sealed. In an attempt to look for ways in which to reduce costs, efforts are directed towards developing new sealants with improved retention and abrasion resistance, investigating new compounds that adhere to the tooth surface through chemical bonds, and studying sealing of early lesions. Currently the NCP is attempting to obtain reliable information on whether a school-based program combining sealants and topical fluoride delivered by dental auxiliaries and preventing virtually all caries would be attractive and cost-acceptable for most communities.

Decrease the Cariogenic Potential of the Diet

Two major objectives are being pursued in this strategy area. The first is to intensively undertake the development of a standard methodology that can be used by dental scientists and food technologists to compare the cariogenic potential of various food items, including snacks and beverages. Direct Program involvement in this area has evolved in order to insure the high level of reliability and interpretability that is required for this standard methodology. The second objective is to continue to develop information on alternative, safe, noncariogenic sweeteners that have (1) sufficient sweetening power, (2) are nontoxic, (3) are reasonably inexpensive, and (4) are thermostable. Research is also being promoted to investigate optimal methods to effect voluntary dietary restriction of sucrose. Interventions which provide potential for testing include those suitable for individual use in the dental office, for use by means of advertising in the mass media, or direct efforts in schools.

Improved Delivery and Acceptance of Caries Preventive Methods

The activities in this strategy are based on two major principles. First, municipal water fluoridation as the preferred public health approach to caries prevention is emphasized. Second, where fluoridation of community water supplies is not feasible, programs of self-application of fluoride designed for school settings are emphasized. Though the target population for these programs is school-age children, because this is the age group most susceptible to caries, the educational activities are conducted through a variety of communication channels and addressed to a number of different audiences, including health professionals, educators, and parents, as well as children. Films, pamphlets, and exhibits are widely distributed and viewed. The NCP also supports applied research in behavioral and sociological aspects of delivery and acceptance of new techniques.

Etiological, Epidemiological, and Physiological Studies

The NCP provides the main support in the United States to develop information on the epidemiology and etiology of caries, on plaque microorganisms, and on the physiology of the host related to caries. Some of the important information that has accrued from these studies includes knowledge about bacterial cell wall composition, role of gut-associated lymphoid tissue in the secretory immune system, transmissibility of S. mutans, interactions between salivary constituents, such as lysozyme and peroxidase, with the surface of the bacterial cell, structure of plaque polysaccharides, function of plasmids and bacteriocins of oral bacteria, and mechanisms of hydroxyapatite demineralization.

Development of Program Effectiveness

The NCP also is involved in a variety of activities to improve research manpower and other related resources, to resolve complex problems involved with setting priorities, and to accelerate R&D processes. Some of these activities have included establishing specialized training programs, determining the factors that inhibit or induce the adoption of new techniques, modeling of long-range effects to evaluate current program investments, and developing techniques for earlier detection of caries in clinical trials.

Evidence of Program Performance

The types of information routinely available and used to monitor program performance include the advice of the NIDR Programs Advisory Committee, the NIDR Board of Scientific Counselors, the National Dental Research Advisory Council, and the NIH peer review process for grants and contracts. In addition, the formal evaluation of the NCP in 1978-79 and the monitoring of the utilization of caries preventive methods and of dental caries prevalence provide information for monitoring program performance. The advice, recommendations, and findings that result from all these efforts are reviewed by the NCP and affect future Program directions.

The NIDR Programs Advisory Committee, reporting to the Institute Director, meets twice yearly with staff of the National Caries Program to review progress and assess plans. Recently part of the meeting was held at the NCP laboratories in the Park Building to discuss research directly with scientists in the Etiology and Preventive Methods Development Sections.

The NIDR Board of Scientific Counselors, again reporting to the Institute Director as well as to the Director of Intramural Research, periodically visits all NIDR laboratories to assess the research in progress and to evaluate the productivity and performance of staff scientists. In addition, NCP intramural scientists make presentations concerning their research to the NIH Deputy Director for Science.

The evaluation of the NCP addressed both the scientific and the organization/management aspects of the Program through use of four scientific panels corresponding to the four NCP strategies, through an organization and management panel, and through a main panel which reviewed the NCP from the perspective of the total Program. Each scientific panel assessed progress relative to the objectives of the strategy and identified future directions for the area. The evaluation included the progress of the research in terms of the following: specific accomplishments, potential of ongoing research, the degree of impasse in the area, relevance of the research to other areas of scientific investigation, and the development of recommendations for advancing progress in the area. The evaluation of each strategy included qualitative and quantitative assessments. The Organization/Management panel employed a number of resources to provide answers to management questions posed by the Institute Director. These resources included structured interviews with NCP staff, NIDR senior staff, NCP/NIDR advisors, and others; and program data including NCP's budget and management processes. The Main Panel's evaluation of the NCP integrated the evaluations of the four scientific panels and the Organization/Management Panel and concluded with recommendations for future directions for the NCP.(4)

All recommendations were reviewed by the NCP staff and the NCP Advisory Committee in light of the existence of NCP relative to other programs within NIDR in this time of economic constraint and scarcity of resources. Several recommendations resulted in the adoption of actual changes. Other recommendations were adapted or led to the maintenance and increased emphasis of existing activities. A few recommendations, such as the restructuring of the NCP to correspond to the strategy hierarchy, were not considered feasible at this time. The NCP rationale for actions taken included a discussion of the Program's actual and perceived needs and opportunities for each recommendation as it related to the scientific, programmatic, training, and budgetary environment.

In response to the recommendations in the Evaluation, the NCP restructured and redefined two of its strategies (II and III), recruited a project scientist to expand the effort on noncariogenic sweeteners through contracts, issued a new request for Cariology Training Grants, currently has a "special expert" working with staff on cost/benefit/effectiveness analysis, is using a standardized method for reporting all NCP-supported projects, and is developing a procedure in which the NIDR Programs Advisory Committee can review the contribution of all program activities to each of NCP's strategies for caries prevention. It is too early for effects of most NCP changes in response to the Evaluation to be manifested. However, assignment of a project scientist to work exclusively on the dietary approach to caries prevention has given definite impetus to this area.

School-based fluoride mouth-rinsing was conducted at 17 sites in the United States and Guam to obtain field data on effectiveness, cost, and acceptability under typical, locally chosen conditions and to demonstrate nationally the usefulness of this approach to caries prevention. The 3-1/2 year demonstration was carried out successfully, with high and often increasing participation rates. All sites elected to continue the programs at their own cost when government support terminated. More importantly, indirect data based on sales of fluoride used in rinse programs indicate that the number of children participating in these programs, at about the 1.7-million level when the program commenced, is now at a level of above 10 million. This increase is attributed mainly to a Program educational effort based on the experience in these demonstrations.

Finally, it should be emphasized that the best evidence of effectiveness comes from direct measures of changes in the prevalence of the disease. Data on national prevalence of caries at the time the NCP was started are provided by the NCHS Health and Nutrition Examination Survey in 1972. Last year, the NCP also surveyed caries prevalence in a national sample. Comparison with the 1972 data indicates at least a 30 percent overall drop in caries in these nine years for individuals 5-17 years old. Reports of several independent surveys of specific local samples confirm this national trend.

Major Issues

The National Caries Program was reviewed by the General Accounting Office in 1977-78, and a report, "Reducing Tooth Decay--More Emphasis on Fluoridation Needed" (HRD-79-3), was issued in April 1979.(5) A main recommendation in the report was that municipal water fluoridation should be promoted further because of its cost-effectiveness and population coverage. With regard to the NCP, the GAO suggested that: (1) criteria should be developed for undertaking NCP demonstration projects, and (2) at least annually the public benefit of tooth decay prevention techniques being funded by the NCP should be assessed. In its response the NCP clarified both issues by describing the exhaustive review of rationale and design criteria that occurred prior to initiating the highly successful demonstration of school-based mouth-rinsing and by pointing out that at approximately yearly intervals it presents all segments of its program to the NIDR Programs Advisory Committee for review.

Major Barriers

There are several major barriers to improved NCP performance. One of these is the geographical separation of the laboratory sections in the Park Building in Rockville from the rest of the Program in the Westwood Building in Bethesda. Through seminars of combined staff, collaborative projects, and other devices, staff interaction is maintained, but at far from optimum level, and only with high expenditure of staff energy and resources that could be employed more effectively.

Another major barrier to performance is the anticipated diminution in funds to support contracts as a result of stabilization of support for grants. Contracts are a crucially important mechanism in a mission-oriented activity like the National Caries Program. Contracts are employed to conduct clinical trials, to develop new diagnostic reagents, to obtain the fabrication of devices, to carry out repetitive but essential measurement, to conduct surveys of health needs, to monitor acceptance of programs, and for literally every step in the translation of research into disease elimination. Without adequate resources for contracts, NCP's prospect for continued effective achievement of its mission is markedly dimmed.

Documentation

1. National Center for Health Statistics. Basic Data on Dental Examination Findings of Persons 1-74 Years, United States, 1971-74. Health and Nutrition Examination Survey (HANES). Vital and Health Statistics, Series 11, No. 214, 1979.

2. "Inflation Incentive for Fluoridation." Refer: FL-115 Dental Disease Prevention Activity, Center for Preventive Services. CDC/HHS, 1979.

3. Health Care Financing Review, HCFA Office of Research, Demonstration and Statistics. Table 2A, Page 17, Summer 1980.

4. "Evaluation of the National Institute of Dental Research National Caries Program." HHS/NIH. November 1979.

5. "Reducing Tooth Decay - More Emphasis on Fluoridation Needed." HRD-70-3. GAO

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Director's Overview

Significance of the Problem

Since the mid-1940s, we have been living in a largely synthetic chemical world. This new world, resulting from our remarkable ability for technological innovation, has resulted in the blessings of an increased standard of living and the potential for harm from ubiquitous chemical exposures.

Compounds once used with little constraint are being linked with severe health effects. Cases in point: DBCP, PBBs, Kepone. Dibromochloropropane (DBCP), an agricultural chemical used to control soil nematodes, was first registered in 1961. Early testing found it caused sterility in rats, but only with high doses and prolonged exposure. Chronic effects and low-dose exposure were not then recognized as serious concerns. Almost twenty years later an alarming incidence of sterility and infertility among a large number of male factory workers exposed to low levels of DBCP was discovered. Subsequently the substance's carcinogenicity was confirmed in a National Cancer Institute animal bioassay. This year manufacturers of DBCP voluntarily agreed to halt production and use of the compound.

In 1973 polybrominated biphenyls (PBBs), used as a flame retardant, were inadvertently added to Michigan cattle feed. Before the accident was discovered, nearly every resident of the State was exposed. No clearly proven correlation between exposure and health problems has been observed so far. It is known from animal studies that 90 percent of an oral dose of PBBs is absorbed and stored in adipose tissue with no appreciable metabolism occurring. A bioassay just completed by the National Toxicology Program (NTP) has produced evidence that PBBs are similar in toxicity to the polychlorinated biphenyls (PCBs). Other animal studies have found that PBBs crossing the placenta are embryotoxic and cause neurobehavioral and immunological toxicity.

Thus, the situation confronting Michigan residents today is that (1) they have a significant PBB body burden in their fat with no known way to reduce it, and (2) animal tests make a strong case for hepatic, immunologic, and carcinogenic toxicities caused by the substance.

Six years ago the Virginia State Health Department found significant levels of the roach and ant poison, Kepone, in the blood of pesticide plant workers and their families. A number of those exposed exhibited neurological, hepatic, and reproductive dysfunctions. At the time Kepone was registered in 1959, toxicity data indicated that it caused "DDT-like tremors." Laboratory animal results in the early sixties, in fact, forecast the tremors and sterility that occurred in 1975. But this information, considered confidential, was never published. In 1977 NIEHS-supported research discovered that Kepone is eliminated very slowly from the body. Treatment with the drug cholestyramine increased elimination from the body sevenfold, and reversed the manifestations of toxicity.

The tragedy of incidents like those involving DBCP, PBBs, and Kepone is that they could have been prevented. If we had more fully comprehended the toxicity associated with these compounds, they might never have entered the marketplace without, at least, stringent controls. Yet, even now, current worldwide capability allows no more than 300 long-term animal tests--the best method we now have for assessing and predicting toxicity--to be initiated each year. With more than 50,000 chemicals currently manufactured, imported, or processed in this country and approximately 500 net additions each year, selecting and testing potentially hazardous compounds in a reasonable amount of time is, at present, impossible. Traditional public health practices of encouraging better hygiene and medical care just do not offer sufficient protection from these new threats to health.

Research in areas of environmental toxicology has provided us with some tools, but they are still very blunt instruments. The challenge is to develop more precise and rapid ways to assess specific toxicities. The ability to identify, evaluate, and predict health effects is limited by our understanding of fundamental biological processes. Any improvement in methods is bounded by advances in basic research. At present, one of the major constraints is that the state-of-the-art permits the study of the effects of gross exposure, as with the DBCP and Kepone incidents; but it is not now particularly helpful in the study of chronic, low-dose exposure to which the general population is susceptible, as in the case with PBBs in Michigan.

As basic and applied research progresses, the body of data which is developing indicates that a significant number of chemicals can be toxic. Needed is a means for determining which chemicals should be accorded priority. With such knowledge, we would have the foundation upon which to build preventive, diagnostic, and therapeutic programs for environmentally related disease.

Program Strategy

The National Institute of Environmental Health Sciences' (NIEHS) research efforts are continuing and extending recent progress in environmental toxicology. Work is being directed toward the development of a rational, systematic approach to estimating the health risks associated with exposure to chemical and physical factors. The Institute conducts and fosters fundamental knowledge development on chemical interaction with biological systems. This involves development of methods to identify and characterize substances known or suspected to be toxic, study of their metabolism and transformation in biological systems, and discovery and description of how these substances damage organs and cells. The information derived is supported when possible by epidemiological studies. Using these toxicological and epidemiological data, quantitative estimates of human risk are developed.

Over the next three to four years, emphasis will be placed on refining existing expertise and expanding into new areas where there is clear scientific need. This effort will be greatly enhanced by completion of a new laboratory facility for the Intramural Research Program. Modest growth is planned in studies looking at the relation between chemical exposure and reproductive effects, in research on ways to identify gene mutations in large populations, in the development of more sophisticated analytical chemistry methods, and in epidemiological studies on the role of environmental factors in chronic disease. Extramural research support will place priority on immunological and specific organ toxicity, health effects from exposure to multiple toxic agents, and development of improved methods for estimation of risk.

The knowledge developed through this fundamental research is applied to toxicological test systems such as those validated and utilized by NTP, in which the Institute plays a central role. In carrying out its charge to identify chemicals potentially toxic to humans, NTP strives to expand toxicological profiles of chemicals nominated and selected for testing; increase the rate of chemical testing; develop, coordinate, and validate series of tests and protocols more appropriate to regulatory needs; and establish a communications network to collect, evaluate, and disseminate information.

Over the next few years, in addition to continuing substantial work in carcinogenesis, NTP will give attention to broadening the characterization of toxic properties to include assessment of genetic, reproductive, and neurobehavioral effects. Expanded effort will be placed on new test method development projects; study of the role of dose, sex, and species on absorption, distribution, and excretion of chemicals; and the understanding of the nature of specific organ system toxicity. Research on developing short-term tests will continue to be emphasized; as these methods are refined, the ability to rank chemicals in order of their potential health risk will be improved.

In addition to the research described, NIEHS provides long-term support to university-based centers to foster research excellence in the environmental health sciences. This support allows these centers to devote multidisciplinary attention to diverse environmental health problems.

To undertake and stimulate research requires not only financial resources but also a core of highly trained and motivated scientists. The breadth and complexity of environmental health problems necessitates development of this research manpower pool in a wide range of disciplines. NIEHS supports research training in environmental toxicology, pathology, mutagenesis, and epidemiology.

In the 14 years since NIEHS was founded, there have been dramatic changes in awareness of environmental health problems as global issues. Cooperation and collaboration with scientists in other countries has grown significantly. NIEHS is participating in several international programs in which it has developed productive relationships. Among the countries it is involved with are China, Egypt, Italy, Japan, and the U.S.S.R. The Institute has also actively participated in many World Health Organization projects. Last year NIEHS was designated as a lead institution of the International Programme on Chemical Safety (IPCS). The purpose of IPCS is to strengthen and expand international activities in the evaluation of the biological effects of chemicals through stimulating cooperation in toxicological research, testing, and manpower development. These efforts are an important aspect of NIEHS' mission of fostering the development of fundamental knowledge about environmental health problems.

Public Health Objectives

The August 1980 Surgeon General's Report on Health Effects of Toxic Pollution found that exposure to hazardous agents in the environment is a major and growing public health problem, the precise dimensions of which are currently impossible to determine. As we uncover new and previously unsuspected environmental threats to health, we discover many substances which have latent toxicity. Thus, as the dilemma of Michigan residents exposed to PBBs implies, we are currently in the very early stages of a health problem which may take years to assess. Yet there are persistent indications that toxic chemicals already are adding to the disease burden of the United States in a significant, although ill-defined way.

Over the next few years, through its Intramural and Extramural Programs and its NTP participation, NIEHS will increasingly focus its efforts on those activities which can contribute to the formulation of a framework for assessing environmental health risks--a capability essential to disease prevention, diagnosis, and treatment efforts. To achieve this NIEHS will:

- Continue fundamental research aimed at discovery of early indicators of chemical and physical injury in biological systems, and at the development of tools sensitive enough to determine this;
- Expand epidemiological studies to improve the identification and assessment of environmentally induced chronic disease in human populations; and
- Intensify efforts to estimate health risks through improving methods for extrapolating from high-dose to low-dose exposure and from animal to man.

If disease prevention efforts are to be supported, they must be based on high quality research prudently applied in protection of the public health. Experience has taught that actions taken without careful review of available information and clear articulation of the uncertainties involved can have painful and costly repercussions, while inaction attributed to the need for more data may be perceived as increasing the risk to human health. As understanding of environmental health issues improves, the Public Health Service can exercise more fully its leadership responsibilities in this area.

NIEHS

FY 1981 Research Highlights

Within the National Institute of Environmental Health Sciences, there are a number of research areas believed to be of major importance in efforts to prevent environmentally related disease.

Intramural

A cohort of 900 North Carolina children is being followed for early low-dose exposure to PCBs and DDT. NIEHS researchers have already found evidence consistent with a placental barrier to these organochlorine compounds in these children. The cohort will be followed for several outcomes, including behavioral development, and breast-fed children will be compared to formula-fed. This project will uncover valuable information regarding low-dose environmental pollutants and young children. In addition, it is breaking new ground in epidemiologic study methodology for measuring low-level exposure to environmental chemicals (using body fluids).

A mutation has been induced in the Drosophila structural gene for one of the subunits of RNA Polymerase II, the enzyme complex responsible for transcription (i.e., activation of the information stored in DNA), and the genetic control of this subunit is being studied. Ultimately, all the subunits will be characterized, and this enzyme's role in normal genetic regulation and development will be determined. Then this knowledge may be used to evaluate how environmental insults alter genetic function and cause disease.

Subtle neurotoxicities have been assessed using behavioral techniques (e.g., sensory, motor, learning, or memory deficits) with PBBs, PCBs, Kepone, triethyl tin, and acrylamide in developing and mature laboratory animals. This will help fill the need for testing environmental exposures for their effects on the human nervous system, and by using a variety of laboratory animals will contribute to our understanding of species-to-species variation and thus strengthen our ability to extrapolate from experimental animals to humans.

Pregnant mice exposed to 2450 MHz microwave radiation for eight hours per day during various periods and at three different power density levels showed no adverse maternal or embryofetal effects at the two lower levels. But those exposed to the highest level, 30 mW/cm^2 yielded significant effects, predominantly cleft palate. This implies that high-dose microwave exposure may be toxic for pregnant women and their offspring, but it also suggests that microwave exposure may not have embryofetal effects at low levels.

National Toxicology Program. A comprehensive battery of rapid, relatively inexpensive tests which will assess a variety of behavioral and neurologic effects in animals has been developed.

Progress has been made in the development and validation of new and improved test methods, particularly for mutagenesis and short-term carcinogenesis.

Individual or small numbers of substances have been evaluated in order to assess the toxic potential of the related class or group of compounds. For example, each of six benzidine-based dyes has been shown to be metabolized in the dog to benzidine, a confirmed human carcinogen. This reaction is believed to be representative of more than 200 benzidine-based dyes of which millions of pounds are commercially produced each year.

Using whole rodent embryo cultures, evidence has been found to suggest that alcohol has a direct effect on the growth of the embryo, particularly of the brain and face. This work may lead to a rapid prescreening teratogenicity test, insight into the mechanism of Fetal-Alcohol Syndrome, and identification of methods to prevent or counteract the deleterious effects of alcohol and other teratogens.

Extramural

New DNA repair pathways have been characterized in E. coli and humans. Among several newly characterized human repair enzymes, one was shown to be inhibited by caffeine; another may be linked to xeroderma pigmentosum. A system for screening agents that bring about DNA repair, and for studying the DNA repair process itself, has been developed.

Mechanistic studies comparing rainbow trout, a very aflatoxin-sensitive species, and Coho Salmon, resistant to aflatoxin, indicate that initial DNA adduct formation may be the rate-determining first step in aflatoxin carcinogenesis. This is the type of detailed information that is required for an in-depth appreciation of cancer pathogenesis, prevention, and treatment.

Toxic red tides caused by Ptychodiscus brevis (formerly Gymnodinium breve) are attributable to at least two toxins which are neurotoxic and hemolytic. Purified crystalline toxin has been characterized, and dose-response toxicity data have been generated in several test systems. Thus, a once mysterious phenomenon is now becoming understood.

Atheroma-like plaques were produced in chickens fed a potent polycyclic aromatic hydrocarbon carcinogen (PAHC). The plaques increased with duration of exposure and, in males, with dose. The plaques were not reversible by cessation of exposure, and the rate of proliferation measurements suggested that the PAHC promoted the growth of preexisting lesions. This is especially pertinent since one theory of atherogenesis holds that the atheroma arises from a clone of a mutated cell.

FY 1982 Program Changes

Overall Budget Policy

The 1982 budget will maintain the number of active research grants at approximately the same level as 1981. The number of competing awards will remain stable. Research Career Programs, Research Centers, and other research grants will be maintained at the current (1981) level. Support for trainee FTEs (full-time equivalents) will also be maintained at the current level. Contract support for targeted research in toxicity test development and validation, and in epidemiologic studies will increase. In addition to mandatory and "built-in" increases associated with the current staff and the occupancy of new research facilities, increases in Intramural Research will permit the expansion of research efforts in carefully selected fields where current research indicates the need and opportunity for advancement. Mandatory increases are included in the budgets of the Direct Operations and Program Management activities.

Research Project Grants

Seventeen additional research project grants will be awarded in FY 1982. The areas in which work will be initiated are:

- Development of accurate predictive tests for assessing human toxicity from exposure to environmental agents (NTP).
- Mutagenesis testing of agents in the environment (NTP).
- Assessment of risk associated with environmental exposures to chemical and physical factors, including ionizing and nonionizing irradiation.
- The effect of environmental agents on target organs.
- The effects of environmental agents upon nutritional and digestive diseases, endocrine function, and immunological competence.

Research Training Grants

The same number of FTEs will be funded in FY 1982:

- Fourteen individual training fellowships and 38 institutional training awards initiated in FY 1981 and earlier will continue to be supported. The number of individuals trained in toxicology will meet approximately 48 percent of the estimated annual demand for toxicologists.
- Seven new individual fellowships will be made. Emphasis will be on training in environmental epidemiology and toxicology. Approximately 60 to 65 percent of the new trainees will be in toxicology, 25 percent in epidemiology, and the balance in pathology and mutagenesis.

Other Research

Six additional contracts will be funded. The areas in which contracts will be initiated are:

- Genetic, reproductive, and neurobehavioral toxicology (NTP); and
- Epidemiology, biometry, and risk estimation.

Intramural Research

The budget request for Intramural represents a dollar increase and 31 positions for scientists and support personnel over the 1981 estimate. A major portion of this funding increase is required to operate and maintain the Institute's new facility at full capacity. The new laboratories will permit NIEHS scientists to work safely with the most advanced techniques available, and will significantly increase available laboratory space. The level of effort of most intramural research will not increase from 1981 to 1982. There are two exceptions to this:

- A health research initiative is included for the expansion of research on reproductive hazards in the workplace in coordination with several other HHS agencies. The initiative will provide incremental funding in 1982 to ongoing research programs. The objectives of the new research are to: improve the understanding of the biochemical processes linked to impaired fertility that is recognized by failure of sperm to penetrate the cell membranes of female germ cells; develop the ability to monitor the seminal fluid of exposed workers in order to assess the likelihood of genetic or reproductive damage; increase the effort in development of immunofluorescence detection of mutant sperm enzymes.

- Research is to be initiated in pulmonary toxicology to find how the cellular components of the small airways and alveoli of the lung react with chemicals to produce the pathology of fibrosis and emphysema that is characteristic of chronic obstructive lung disease. In addition, the recent remodeling of the NIEHS inhalation exposure facility for small animals has provided redesigned inhalation chambers that are carefully controlled and monitored on-line by computer programs. These facilities will now be brought under the supervision and management of the new inhalation toxicology head and will become available for a variety of chemical inhalation exposure experiments within the research programs in the NTP and the Intramural Research Program.

Funds will allow NIEHS to expand its contribution to NTP in:

- Applied test method development in immunology, chemistry, and behavioral and neurological toxicity;

- Inhalation toxicology; and

- Pharmacokinetics.

FY 1983 Program Changes

In FY 1983, NIEHS plans to begin using a new activity structure to describe its research programs. This modification has been undertaken for several reasons:

- The environmental health sciences are maturing. Public awareness of environmental health issues is growing. These factors prompted us to describe ourselves in a manner more reflective of the state-of-the-art, and more informative to those concerned about environment and health.

- Progress in health programs has improved our ability to focus in on areas of particular significance.

- Involvement with the National Toxicology Program (NTP) has precipitated the necessity for clearer distinction among program activities.

In general, these new categories are considered to be more appropriate to, and descriptive of, NIEHS efforts. Initially these rubrics will not be applied to intramural programs; however, a long-term goal is integration of those activities into this framework.

The new categories are as follows:

- Characterization of Environmental Health Hazards. This category includes research focused on development of sensitive and accurate techniques which allow the analysis and characterization of potentially toxic substances. It also includes work on how and at what rates chemical/physical agents enter the body, are stored, and are metabolized and excreted.

- Biological Response to Environmental Hazards. Of prime concern in research in this category is identification and understanding of biological damage resulting from chemical or physical factor insult. This includes description of the mechanisms of toxic change and assessment of toxicity in a range from the whole organism to the cellular and molecular level.

- Applied Toxicological Research and Testing. NIEHS research programs serve as a link between the study of chemical disruption of fundamental biological processes and the application of this knowledge in toxicological test systems such as those validated and utilized by the NTP. The portion of the NIEHS and NCI research effort dedicated to the NTP is the Toxicology Research and Testing Program. Only activities in this Program are included here. However, due to management constraints relevant neurobehavioral toxicology, indirect operational and support costs, and corporate NTP program management staff are not included in this budget category.

- Biometry and Risk Estimation. The ultimate focus of the NIEHS mission is towards the development of quantitative estimates of human health risks from exposure to environmental factors. Having identified a hazard, characterized the interaction of that hazard with a biological system and the damage wrought by the hazard, the data are analyzed and an estimation of risk is formulated. Work in this category involves biostatistical research and epidemiological studies directed toward the development of dose-response relationships.

- Resource and Manpower Development. The activities in this category remain the same; only the name has been changed.

- Intramural Research. This category remains basically the same with the exception that toxicological research and testing, and biometry and risk estimation activities have been separated out.

- Direct Operations. This category is unchanged.

- Program Management. This category is unchanged.

Overall Budget Policy

The 1983 budget request maintains the number of active research grants at approximately the same level as 1982. The number of competing awards declines slightly. Support for Research Centers and Other Research will be modestly increased from the 1982 level. The number of Research Career Program awards declines slightly. The number of full-time equivalent trainees will remain at approximately the current level; individual awards will increase while institutional support will decline slightly. Contract support for targeted research will increase. Increases in Intramural Research will be used to expand work in carefully selected areas of unmet scientific need. Mandatory increases are included in the budgets of the Direct Operations and Program Management activities.

Research Project Grants

- In addition to 218 grants awarded in 1982 and before, 100 competing awards will be made in 1983. This represents 39 percent of approved applications and funding of applications through a priority score of 230.

- Within the constraints of scientific merit, priority will be given to applications in the following scientific areas: Multiple exposure to chemical and toxic agents, immunotoxicity, and organ toxicity. Review and refining of programs will continue through 1983 to permit NIEHS to focus resources on new research emphasis areas as recommended by the National Advisory Environmental Health Sciences Council.

Research Training Grants

- NIEHS will support 27 toxicology training grants, 10 epidemiology training grants, 7 training grants in pathology, 1 in mutagenesis, and 35 toxicology fellows. The annual output rate of toxicologists would then be 125.

Other Research

- Support for all ongoing centers will increase to permit continuation of research at a level modestly increased from the 1982 award level.

- Two new Research Career Development Awards will be made.

- In addition to ongoing contract-supported projects, new targeted research projects in the fields of epidemiology and risk estimation, and test development projects related to reproductive toxicology, fertility assessment, and neurological toxicology will be initiated.

Intramural Research

Additional dollars and 20 positions are requested above that required to maintain the 1982 level of intramural research. This will be used to expand work in the following areas:

- Studies on reproduction, which began in 1982 with specific orientation toward workplace exposure to include basic studies of the role of environmental agents in birth defects, fertility, and the molecular mechanisms of damage to sperm and egg cells.
- Epidemiological studies of environmental factors in chronic diseases, such as kidney and chronic, persistent respiratory diseases; identification of developmental problems or other morbidity in populations of infants or small children; and development of methods to utilize vital statistics to measure the effects of environmental factors.
- Research on ways to identify significant gene mutations in large populations, with specific attention to mammalian cell mutation at the molecular level.
- Work in environmental chemistry, specifically in the development of analytic methods--such as nuclear magnetic resonance and mass spectroscopy--which are important in the identification, characterization, and quantification of environmental agents including synthetic organic compounds of unknown or suspected toxicity.

Toxicology Research and Testing Program

- Twenty-five new comprehensive toxicology tests will be initiated in 1983.
- Contract-supported new test development projects in reproductive toxicology and fertility assessment, and in neurological and behavioral toxicology will be initiated.
- 1982 levels of effort for combined NIEHS and NCI activities in test development, behavioral toxicology, basic research, and test monitoring will be supplemented with additional efforts in reproductive toxicology. Additional positions will be used for research relevant to the development of rapid screening methods and rapid bioassays and for research on the development of principles for testing and for validating test results.

Potential Impact for Program Changes, FY 1983-85

As NIEHS looks beyond 1982, we anticipate that certain institutional and program changes occurring in that year will be having an effect:

- Occupation of the new facility will be completed. Space limitations on program development will be relieved and modest expansion of research efforts which have been planned for several years can be undertaken.

- The Institute's reorganization should be in effect:

  --Transfer of the NCI Bioassay with establishment of a Toxicology Research and Testing Program (TRTP) will provide a closely integrated NIH response to NTP's responsibilities. It will allow more effective management of NCI and NIEHS resources, and continued broadening of bioassay efforts to consider toxic endpoints other than cancer.

  --The Biometry Branch of the Intramural Program will be established as a separate Program of Biometry and Risk Assessment. It will provide an Institute wide focus for biostatistical and computing services and also serve to concentrate NIEHS and NTP efforts in epidemiology and quantitative estimation of health risks.

- The new budget activity structure to be readied in 1982 will be implemented in FY 1983, improving presentation of the NIEHS budget. It will provide a more reasonable and logical sequence to Institute activities, be more descriptive of our program, and consistent with the reorganization plan.

The environmental health issues which we anticipate to be prominent into the mid-1980s require that we develop a science base with the following critical elements:

- Improved analytical methods for identifying, characterizing, and quantifying environmental agents.

- Opportunities for growth in research areas of neurobehavioral, pulmonary, reproductive, and immunotoxicology.

- Methods for inexpensive screening of suspect substances, particularly short-term tests.

- Methods for assessing the toxicity of chemical mixtures.

- Screening techniques for assessing human exposure.

- Better methods for quantification of health risks utilizing toxicological information.

These institutional changes and research needs provide the parameters within which NIEHS will operate over the next several years.

NIEHS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Institute of Environmental Health Sciences

DATE: FEB 13 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I was pleased to note the progress that has been made in the construction of the new permanent facilities in Research Triangle Park. It was especially informative to review with you the plans for the effective utilization of these new facilities. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

D S Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

As the NIEHS prepares to occupy its permanent facilities in Research Triangle Park, N.C., it is becoming apparent that future developments will be focused on (1) development of accurate predictive tests for human toxicity of chemical agents; (2) understanding the nature and extent of the toxicity of chemicals and their mechanisms of action, and evaluating their effects in terms of impact on human health; (3) conducting epidemiological studies dealing with a broad range of environmental exposures; and (4) assessing the extent of hazard that exposure to these chemicals poses for humans.

Impact of Stabilization

- There will be a nominal increase in the number of research project grants in 1981 and a slight increase in 1982.
- Program projects will increase only slightly in 1981 and 1982.
- Support for Marine and Freshwater Biomedical Research Centers and Environmental Health Science Centers will remain at the 1980 level.
- The number of R&D contracts will increase slightly in 1982 over 1981. This will prohibit needed expansion in R&D contracts related to the National Toxicology Program (NTP).
- Overall support for training will decline slightly in 1981 and 1982. Individual awards will show a modest decline; institutional awards will remain essentially at the 1980 level. This will prohibit needed expansion in (a) mid-career development awards (K07), and (b) training DVM's in environmental pathology research.
- The number of positions increases significantly in FY 1981 and again in FY 1982. In 1981 these increases are to provide the second block of positions required to permit activation of the new facility. The increase in 1982 primarily reflects support for non-NTP positions for expansion of research on the toxicity of inhaled fibers, gases, and aerosols; monitoring sperm cell mutations;and other reproductive toxicology studies.

Permanent Facility

- The permanent facilities of NIEHS in Research Triangle Park, N.C., under construction since 1977, are nearing completion. Support facilities (power plant, shops, warehouse) are completed, office areas will be completed in March 1981, laboratory areas are scheduled for completion by July 1982, and space off the North Campus (except for warehouse) should be relinquished within one year. However, delays in construction have caused millions of dollars of delay claims for which liability has not been resolved.

- Dollar increases are needed for utilities, support services, equipment, and final alterations.
- Positions provided in 1980 and 1981, which are especially needed for engineering, animal care, and lab support functions, must be unfrozen to complete support staffing for the new facility. Twenty-six positions are needed to complete the supporting staff for the new animal facility at the current level of research activity.

National Toxicology Program

The main issues facing the NTP and toxicity testing in general are (1) shortcomings created by the existing organizational arrangement, (2) the need to develop less expensive and more rapid methods that may obviate the need for lifetime animal tests, (3) the difficulty of determining the toxicity of two or more compounds acting in combination, and (4) the problem of determining at what rate and how new compounds should be tested.

Action Item

The NIEHS will develop a position paper which will (1) propose a minimal number of new compounds which, on the basis of scientific need, should be tested for toxicity; (2) describe the rationale for the selection of such compounds; and (3) provide a discussion of the broader scientific context in which toxicological testing is conducted, including a statement on the importance of efforts to develop new and improved testing methods and the need to balance the resources devoted to testing against those required to develop new tests.

NIEHS

Administrative Constraints

Statement of Issue

The continual application of ceilings in three critical areas--travel, consultant services, and conferences--and the limitation in fourth quarter procurements are having serious adverse effect on the NIEHS's ability to fulfill its mission. Also the application of the full-time equivalent system for managing full-time employment promises to eliminate a significant number of vacant positions necessary to respond to increased program responsibilities.

Discussion of Issue

- Over the past few years NIEHS programs have grown. NIEHS has been assigned additional responsibilities related to the NTP and the imminent completion of its new research facilities.

- At the same time these program expansions and responsibilities have meant that expenditures in areas such as travel, consultant services, and conferences have tended to increase. The imposition of ceilings based on prior levels of program activity is unrealistic given the broadening of NIEHS responsibilities.

- During the same period the appropriations process has frequently not been completed until after the start of the fiscal year and additional requirements have stretched out the contracting and procurement processes. As a result, it is often impossible to plan the expenditure of new money prior to the fourth quarter of a fiscal year. Because of this, efforts to reduce last minute contracting can result in unwise shortening of the time available for procurement planning.

- NIEHS was allocated 55 new positions in the FY 1980 budget process. The 1981 continuing resolution level includes funding and authority for 55 additional positions. These positions were provided for occupancy and operation of the new research facility in response to specific plans NIEHS prepared and submitted to Congress in the fall of 1979. Even with specific exemption from hiring ceilings for facilities engineering positions, NIEHS has not been able to fill all of these vacancies,as well as the vacancies existing prior to the allocation of the 55 positions in 1980 because of the President's limitation on employment. NIEHS has entered calendar year 1981 with a significant number of unfilled vacancies.

- The new full-time equivalent system of controlling employment has the effect of eliminating unfilled vacancies. This will leave major gaps in staffing for our Intramural Programs, the NTP, and supporting services necessary to open and operate our new facility.

Alternatives and/or Suggested Position

NIH should request additional ceilings and relief from hiring restrictions on the basis of the programmatic requirements of the NTP and the completion of NIEHS permanent facilities. NIEHS recognizes the uncertainty regarding levels of employment. However, it is important that the urgency of Institute staff needs be understood. NIEHS cannot fully meet the obligations related to NTP and its new facility unless it can hire the staff to carry them out. NIEHS will continue to rely on NIH support in removing these constraints.

Permanent Facility

Statement of Issue

- The new research facilities of NIEHS, under construction since 1977, are nearing completion.

- Operating the new facilities continues to demand a sizable investment of funds and positions.

- Delays in construction have precipitated a situation in which several millions of dollars of delay claims have not been adjudicated.

Discussion of Issue

- Completion and occupancy timing.

  --Support facilities (power plant, utilities systems, shops, and warehouse) are completed and undergoing final check-out.

  --Office areas (modules A and B) will be occupied in March.

  --Laboratory areas (modules C, D, and E) are scheduled for completion by July 1982.

- Resource needs.

  --Dollar increases are needed for utilities, support services (security, housekeeping, and messenger service, for example), equipment, and final alterations.

  --Positions continue to be needed for facilities engineering, animal care, and laboratory support functions planned for in-house staff.

- Delay claims.

  --The resolution of the liability for delays should be more aggressively pursued. This is the responsibility of the HHS Regional Engineer.

  --The existence of these unadjudicated claims strains relationships between the Government Project Manager and the Construction Manager, making it difficult to accomplish minor changes.

  --The cost of claims settlement cannot be accurately estimated.

Suggested NIH Position

- In the allocation of resources, NIH should bear in mind that decisions were made and plans started on the assumption that positions and funds would be available in fiscal years 1980 and 1981.
- Construction progress, although delayed, is still moving along. NIEHS faces grave problems if recently established limits and constraints prevent accomplishment of plans for occupancy and operation. Decision-makers at OMB, HHS, and PHS must be made aware of these plans and commitments.

PROGRAM PERFORMANCE SUMMARY

NATIONAL TOXICOLOGY PROGRAM

Program Description

Health Problem Being Addressed

The central reason for the establishment of the National Toxicology Program (NTP) is to protect the health of the American public from damage by exposure, often inadvertent, to toxic environmental chemicals. We know that many human diseases can be traced to chemical exposure--lung cancer to asbestos, arsenic, bis(chloromethyl)-ether, and other agents; liver hemangiosarcoma to vinyl chloride; mesothelioma to asbestos; male sterility to Kepone and dibromochloropropane; and neurologic disease to Kepone, methyl mercury, lead, and methylbutyl ketone. Preventing human exposure to such chemicals can prevent human disease; thus, the NTP is an important element in the preventive health initiative of the Department of Health and Human Services (DHHS).*

Lacking precise numbers, we must estimate the extent of this chemical exposure--the numbers of chemicals, the intensity of exposures, and the number of people exposed. It is estimated that there are 40,000 to 60,000 chemicals in commerce today in the United States. The production of about 5,000 of these is greater than one million pounds per year, suggesting the possibility of widespread and intense exposure. There are around 2,000 to 3,000 food additives and about 4,000 drugs, medications, and components of drugs. There is known human exposure to at least 1,200 additional compounds found in household products. Moreover, the number of chemicals in commerce is increasing by about 500 to 1,000 new compounds each year.

The universe of chemicals to which we are exposed is therefore so large that it might appear impossible to prevent human exposure to toxic chemicals. But the key word is toxic. While many chemicals can be shown to be toxic--that is, ultimately harmful at some dose or schedule--most are relatively nontoxic, so that few, if any, controls are necessary to protect human health. For many other chemicals, moderate controls or restrictions--still allowing some exposure--will be adequate. Thus, strict control of only a small fraction of the chemicals in our environment is necessary for health protection and disease prevention.

Program Development

NTP is a result of concerns that have affected not only the Executive Branch, but also the Legislative Branch of Government. In the decades of the sixties and seventies, information was developed that indicated many environmental chemical agents interfere with cell replication, and thus might have an adverse effect on genetic inheritance. This resulted in great energy and resources being invested in developing means to assess rapidly and inexpensively the toxicity of these compounds. Further, information was developed that provided presumptive evidence that many compounds which are mutagenic may also be carcinogenic. Thus the testing of compounds for mutagenic activity holds some promise for decreasing the number of compounds that require testing in a complete cancer bioassay, thereby resulting in significant savings of time and resources.

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*At the time of NTP's establishment, DHHS was known as the Department of Health, Education, and Welfare (DHEW); however, DHHS will be used hereafter.

Throughout this period there was major Congressional activity aimed at providing legislative tools for the regulatory agencies to reduce or prevent exposure to hazardous substances. This new legislation (including the Toxic Substances Control Act or TSCA) greatly increased the need of the regulatory agencies to know more about the toxicity of environmental agents. In addition, as has been illustrated dramatically by the controversy surrounding saccharin, the regulatory agencies realized they must be able to interpret the results of laboratory and animal tests in terms of their relevance to humans--thus, the recent upsurge of interest in the area of risk assessment.

As a result of their specific regulatory or research needs, the various Federal agencies began to develop or intensify test programs in a variety of areas. Most of these test programs were limited in scope, and therefore did not take into account either exposure sources or toxicities other than the ones of specific interest to the sponsoring agency. In addition, the research and regulatory agencies often were looking at the same compounds, but for different reasons, thereby contributing to the appearance of overlap and duplication among their programs. Thus, in looking at the broad field of toxicology testing, it became apparent that the Nation's testing capacity was not being used to best advantage, and would benefit from better coordination and program integration.

It was against this backdrop of scientific, regulatory, and Congressional concerns that the Secretary, HHS, established the NTP by administrative action on November 15, 1978.

In structuring the new program, the Secretary wanted to meet two overriding needs: (1) to integrate DHHS activities in order to permit the most effective use of the Department's resources and consolidate expertise in those areas of science required to determine the full toxicologic potential of a given compound, and (2) to establish an effective dialogue between the research and regulatory agencies so that stronger links could be forged between toxicology research and the needs of the regulatory community.

NTP was envisioned as a means of bringing together the Department's major toxicological research and testing activities--which all had been developed to support different organizational missions--to mount a coordinated attack on the problems of toxic chemicals. Because there was not general agreement within the Department on how best to organize these activities, the Secretary, as an interim measure, decided to establish a program funded through voluntary allocations from the relevant DHHS agencies that would be managed by a Program Director.

As a result, the NTP consists of the relevant activities of the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), the Food and Drug Administration and its National Center for Toxicological Research (FDA/NCTR), and the Centers for Disease Control/ National Institute for Occupational Safety and Health (CDC/NIOSH). Resources for the program originate from the budgets of these contributing agencies.

The NTP activities to which these contributing agencies allocate their resources are planned and carried out as a coordinated whole under the leadership of a Program Director, who also is Director of NIEHS. For purposes of the NTP, the Program Director reports to the Assistant Secretary for Health, HHS.

So that regulatory concerns would be joined with the program, the Secretary invited the Occupational Safety and Health Administration (OSHA) of the Department of Labor, the Environmental Protection Agency (EPA), and the Consumer Product Safety Commission (CPSC) to participate in the NTP. These agencies, along with the NIH and the Office of the Assistant Secretary for Health, HHS, are the participating agencies of the NTP.

The Executive Committee, NTP's major advisory group, is made up of the heads of both the participating agencies and the contributing agencies. It is this unique NTP aggregation that assures continuing input from the research and regulatory agencies into critical phases of NTP operation, including nomination, selection, and prioritization of chemicals to be placed on test, determination of priorities for test method development and validation, and oversight of program planning and balance.

In total, this organizational arrangement brings together the Department's expertise in toxicology and the regulatory agencies' experience and concerns in order to permit a consolidated approach to research on, and testing of, chemicals. In this way, information needed for controlling hazardous substances and for protecting the health of the American people can be developed.

At about the same time the NTP was established, Congress, through the Community Mental Health Centers Act Amendments (P.L. 95-622), gave the Secretary, HHS, authority--in addition to the broad authorities outlined in Section 301 of the Public Health Service Act--to conduct and support studies and testing of substances for carcinogenicity, teratogenicity, mutagenicity, and other harmful biological effects.(1)

Then, during the FY 1980 appropriation hearings, Congress once again turned its attention to the NTP and the problems it was designed to address. It commended the Secretary, HHS, for establishing the NTP and provided $23 million for NTP, of which $17 million was derived from reprogramming funds within the NCI budget. These funds were to enable testing of an additional 100 compounds in the carcinogenesis bioassay.(2) The following year, during appropriation hearings for FY 1981, Congress noted that current efforts of the NTP aimed at establishing scientific principles, standards, and new reliable techniques for toxicity testing should emerge as its central role as the burden of testing compounds is gradually shifted from public agencies to the private sector under TSCA.(3)

The next step in NTP's evolution was taken when, on July 14, 1981, the HHS Secretary approved the transfer of the NCI carcinogenesis bioassay program to the NIEHS. This completed the process that began with the assumption by NIEHS in FY 1980 of administrative responsibilities for the activities of the bioassay program. Since the inception of the NTP, the NCI and NIEHS have worked to strengthen cooperation between, and integration of, the two NIH programs. In the spring of 1980, in recognition of the need to bring these two programs closer together, the Directors of the NIH, NCI, and NIEHS agreed to transfer the bioassay program to NIEHS in order to integrate fully the NIH components of the NTP. With the Secretary's approval of the move, the chemical toxicity testing efforts shifted from NCI, and the testing and test development activities of NIEHS will be managed as an integated whole under the Toxicology Research and Testing Program (TRTP), headed by the NTP Deputy Director. The TRTP combines all NIH/NTP activities under NIEHS management; and it is composed of six branches: Program Operations, Program Resources, Carcinogenesis and Toxicology Evaluation, Systemic Toxicology, Cellular and Genetic Toxicology, and Chemical Pathology. TRTP is responsible for all NIH/NTP activities; but the NCI continues to be involved in the NTP through the Executive Committee, the Board of Scientific Counselors, and the operational committees. This administrative arrangement eliminates operational and administrative problems created by two Institutes having simultaneous management responsibility for the bioassay program; reduces the difficulty of recruiting professional-level staff by eliminating the uncertainties related to the geographic location of, and managerial responsibility for, the program; and consolidates approximately 87 percent of the NTP's resources under the Program Director's control. Thus, the majority of NTP's budget will be allocated from one source, which will aid in program planning.

On July 15-16, 1981, the House Committee on Science and Technology, Subcommittee on Investigations and Oversight, held the first oversight hearings on the NTP. The Subcommittee met to evaluate the progress made during NTP's first three years of existence, and it commended the DHHS and the NTP for progress to date. It further noted its pleasure that the NTP has proven to be an effective effort in coordination and collaboration among the participant agencies, and said that the NTP may prove to be a model for carrying out interagency programs and developing new approaches to health problems.(4)

During those oversight hearings, the HHS Assistant Secretary for Health announced his intention to review the status of the NTP in order to make recommendations to the Secretary regarding the organization and permanence of the NTP structure. On October 5, 1981, the Assistant Secretary for Health completed his review and recommended to the Secretary that he establish the NTP as the permanent mechanism for coordinating DHHS toxicological research and testing and schedule a management review after two years. The Secretary has approved this recommendation, ending the experimental phase of the program design. This should facilitate recruitment of professional-level staff, as well as the provision of a stable organizational focus for personnel employed in NTP-dedicated activities.

Program Funding and Staffing

Since its establishment, the NTP has been funded through voluntary dedication of resources by its "contributing agencies," FDA/NCTR, the NCI, the CDC/NIOSH, and the NIEHS. However, because the HHS Secretary approved the administrative transfer of the NCI carcinogenesis bioassay program to the NIEHS on July 14, 1981, NCI and NIEHS funding for NTP is combined under NIEHS in Table 1 on the following page. In addition, because NTP was established in November 1978, no resources are shown for FY 1978.

Program Objectives and Activities

Program Objectives

The goal of the National Toxicology Program is to strengthen DHHS activities in the testing of chemicals of public health concern, as well as in the development and validation of new and better-integrated test methods. Specific goals for the program are to:

- Develop and validate new test methods for use in determining the full toxicologic potential of compounds;
- Broaden the toxicological characterization of the chemicals being tested;
- Increase the rate of chemical testing, within the limits of available resources; and
- Communicate program plans and results to government agencies, the medical and scientific communities, and the public.

Current Program Activities

Because of the similarity of interests of the contributing agencies, and the broad range of capabilities available to the NTP, the NTP determined it initially would concentrate on consolidating this toxicological expertise so that it could detect and examine as many as possible of the various toxic effects a given chemical may produce. To this end, the NTP has developed two extensive program areas: toxicologic research and testing, and coordinative management. These activities build on the contributing agencies' expertise in toxicology, extensive laboratory facilities and animal testing skills, and experience with carcinogenesis bioassays and mutagenesis tests. Through them, the NTP has been able to take a comprehensive approach to the problems of chemical toxicity and carry out activities that could not have been initiated without NTP's pooling of resources.

The toxicologic research and testing activities developed by NTP are concerned with cellular and genetic toxicology, carcinogenesis, general toxicology, chemical disposition, immunological toxicology, neurobehavioral toxicology, pulmonary toxicology, and reproductive and developmental toxicology.

Table 1

National Toxicology Program by Contributing Agency

(Dollars in Thousands)

	1979 Actual		1980 Actual		1982 Estimate		1982 Estimate	
	Amount	Positions*	Amount	Positions*	Amount	Positions*	Amount	Positions*
National Institute of Environmental Health Sciences**	$35,989	99	$54,802	133	$58,212	140	$63,814	140
Food and Drug Administration/National Center for Toxicological Research	7,000	47	6,300	43	6,140	44	6,922	53
Centers for Disease Control/National Institute for Occupational Safety and Health	4,700	20	4,608	25	4,100	34	4,100	34
Total	$47,689	166	$65,710	201	$68,452	218	$74,836	227

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*NIEHS positions are permanent full-time budgeted positions; FDA's and CDC's represent man-years.

**Of the amounts shown for NIEHS, the following were appropriated to NCI prior to the Secretary's approval of the transfer of the NCI Carcinogenesis Testing Program to NIEHS on July 14, 1981:

1979		1980		1981		1982	
Amount	PFT***	Amount	PFT	Amount	PFT	Amount	PFT
$25,812	52	$43,495	80	$45,686	87	$49,034	87

***Permanent full-time positions.

Overall, these activities are directed toward developing and validating new and better-integrated test methods to define toxicity, as well as toward testing chemicals of public health concern. During FY 1981, the NTP focused on developing or validating new or improved test methods in 10 areas: teratology, neurobehavior, fertility and reproduction, immunotoxicology, renal function, carcinogenicity, kidney function, quantitative risk assessment, mutagenesis, and pulmonary function. In conjunction with this methods development and validation activity, NTP started 40 chemicals in the prechronic phases of the bioassay; completed approximately 370, and started 460, genetic toxicology tests; and concluded inhalation toxicology studies on 6 chemicals, immunotoxicology studies on 25 chemicals, and neurobehavioral toxicity studies on 10 chemicals. It also developed the capability to study about 20-25 chemicals per year for reproductive and developmental toxicity and between 15-20 chemicals per year for chemical disposition.

The NTP coordinative management activities serve primarily to facilitate and support the research and testing activities, as well as to provide information on program plans and progress. They include chemical nomination and selection, laboratory management, collaborative services, planning and coordination, quality assurance-good laboratory practices, chemical and pathology repositories, data management and analysis, laboratory animal medicine and quality control, laboratory health and safety, and information generation and dissemination. It is through these activities that NTP ensures it has a coordinated communications network to collect, evaluate, and disseminate toxicologic information concerning data compilation, test results, methods development and validation, and other NTP activities. During FY 1981, the NTP published and distributed--among other items--the NTP FY 1981 Annual Plan, the first Annual Report on Carcinogens, improved toxicology and carcinogenesis bioassay reports, computerized listings on all chemicals in various stages of testing, issues of the NTP Technical Bulletin, and notices of all major NTP activities.

With future budget projections and the state-of-the-art for toxicology as the basis for planning, the NTP has determined that it must concentrate on (1) stabilizing the number of compounds it can put on test in each of its activities, and (2) focusing its test method development and validation efforts in those areas most urgently needed, as well as those areas closest to fruition.

While NTP will be shifting from a relatively large testing program to a smaller, more focused one, it also will be attempting to improve and increase the information to be gleaned from its testing. This will be accomplished through the continued improvements in experimental test designs expected as a result of NTP's investigation of dose and experimental animal model parameters and through adaptation of test protocols to specific chemicals. Through these means, NTP will be able to develop data more useful for low-dose toxicity extrapolation, while preserving the detection potential of the current screening format.

In the area of methods development and validation, the NTP will concentrate on (1) completing validation of test methods now under development, (2) developing the sophisticated research tools and knowledge needed to study the urgent problem of chemical mixtures, their interactions, and their toxic effects, and (3) developing methodologies needed to permit low-dose extrapolation from test species to other species, including humans. In regard to the latter, NTP already has initiated a program in DNA repair to complement its mutagenicity screening so that such testing will approximate more closely the human situation.

In coming years, the NTP expects to be able to devote more of its resources and attention to the critical task of test method development and validation.

Evidence of Program Effectiveness

Types of Information Used To Monitor Program Performance

Quantitative measures for NTP program performance are provided through the computerized management status system NTP has developed for chemicals in various stages of testing. This system permits collection of data in a timely fashion on the status of each animal carcinogenesis experiment in every one of the NTP laboratories. It provides information on how many chemicals were started on prechronic and chronic tests, when they were started, the names of the chemical managers, where the chemicals are being tested, the route by which they are being tested, the species of animals used in the experiments, results of the Pathology Working Group reviews, the status of technical report publication for the respective chemicals, and a summary of test findings. A status report generated through the system is produced each month. This report is distributed monthly to core NTP staff and quarterly to about 650 individuals and groups outside the program who require information about movement of chemicals through the NTP. The DHHS Operations Management System (OMS) also monitors monthly and quarterly progress of the carcinogenesis bioassay and mutagenesis testing programs, resulting in additional quantitative measures of the program's performance.

Qualitative measures of NTP's performance are developed through the extensive peer review system the NTP has developed. Peer review of NTP program performance is a multilevel process, involving review of project concepts, project proposals, and completed technical bioassay reports. This review is carried out at different times by the NIH/NTP Steering Committee, the Board of Scientific Counselors, the Environmental Health Sciences Review Committee, and the Technical Reports Review Subcommittee of the Board of Scientific Counselors, supplemented by an ad hoc panel of expert reviewers. Through this extensive review, the NTP is assured that its program efforts are of high quality and relevance, which are important measures of program performance.

NTP also has established an elaborate system of quality control in order to ensure the effectiveness of its program. This system involves the following: Chemical Managers who ensure that chemicals are thoroughly evaluated scientifically, Experimental Design Groups which make certain that testing is designed to measure relevant endpoints, Pathology Working Groups which secure an independent pathology laboratory's examination of all target organ slides and 10 percent of all others, the Data Analysis Group which is responsible for confirming that studies are designed properly, the Quality Assurance-Good Laboratory Practices Section which establishes that the bioassay reports accurately reflect the data found, and Laboratory Monitors who are responsible for the conduct of the studies.

Evidence Relating Directly to Stated Objectives of the Program

Because much of the testing undertaken by the NTP involves multiyear experiments, and because the NTP is only three years old, it will be some time before truly meaningful evaluations of its total effectiveness can be made. However, there are indications of initial success by NTP in responding to its four broad objectives.

In the area of developing and validating new test methods for use in determining the full toxicologic potential of compounds, NTP has made significant strides. It has started a major initiative in developing short-term prescreens for teratogenesis, and it will complete validation of the neurobehavioral test battery shortly. NTP expects to complete validation of the fertility and reproductive assessment assay in about two years, and it has begun an interlaboratory testing study of the immunotoxicology battery of tests. NTP developmental work on renal function assays has shown that existing tests, for the most part, are not very sensitive; efforts to overcome this deficiency will continue. NTP has let two contracts for a short-term lung adenoma test for carcinogenicity that, if validated, should produce results in six months rather than two years. NTP also is incorporating clinical chemistry endpoints into more of its studies in order to increase the toxicologic information to be gleaned from its testing program. Also as part of NTP's efforts to develop new test methods, scientists in the program are studying various dose levels and animal models in the search for the best carcinogenesis bioassay design. They are working to develop better methods for quantitating risk for the human population; and they are examining methodologies to detect heritable genetic effects, impaired kidney and pulmonary function, and neurobehavioral toxicity for modifications. NTP has been able to increase the portion of its resources allocated to test methods development and validation from 14 percent of its budget in FY 1980 to 22 percent in FY 1982.

With regard to broadening the toxicological characterization of the chemicals being tested, NTP has expanded its testing design to include an integrated approach involving mutagenesis, chemical disposition, immunotoxicology, clinical chemistry, and reproductive and developmental toxicology screening, in addition to the long-term carcinogenesis bioassay. Thus, in the NTP, chemicals no longer are tested only for their carcinogenic potential, but also for toxicologic effects other than cancer (e.g., damage to genes and chromosomes and to critical targets such as the lungs, liver, and immune and nervous systems). Currently, NTP also has begun to integrate renal and neurobehavioral toxicity studies into its general toxicology screen. Significantly, about 70 percent of the 40 bioassay starts in FY 1980 included special toxicology studies in the NTP prechronic testing phase. All chemicals started in the prechronic phase of the bioassay in FY 1981 had an expanded design. The goal of this work is to ensure that all major toxic effects have been identified for each chemical to be studied on chronic tests.

Budget resources for the NTP have changed substantially from the projections made when the program was first organized, and this has affected the NTP's ability to increase the rate of chemical testing. Original plans estimated that NTP's resources would increase yearly so that the number of chemicals it could start on test in the prechronic and chronic bioassay and in the special studies could be increased significantly, while at the same time a broad range of test methods could be developed and validated. Budgetary constraints have required modification of the program's original plans. For example, the number of chemical starts projected for the prechronic phases of the bioassay in FY 1981 had to be reduced from 75 to 40.

Even with these constraints, however, the NTP has been able to increase the capability of its genetic toxicology testing program so that it was able to complete 261 tests in FY 1980, compared with 79 tests in FY 1979. In FY 1981, NTP completed 366 and began 460 genetic toxicology tests. It also has developed the capability to study about 20-25 chemicals per year for reproductive and developmental toxicity and between 15-20 chemicals per year for chemical disposition. During the FY 1979-1981 period, NTP completed 43 chemical disposition studies. By FY 1982, NTP expects to be able to study the distribution, metabolism, and excretion of most of the chemicals selected for carcinogenesis bioassays. This will aid in selection of proper dosage and dose regimens for the two-year bioassay. During FY 1981, NTP also completed inhalation toxicology studies on 6 chemicals, immunotoxicology studies on 25 chemicals, and neurobehavioral toxicity studies on 10 chemicals.

Because the end product of the NTP is information, communication is critical to program success. For this reason, NTP has developed a number of mechanisms to aid it in improving the flow of information to the public. Among these are the NTP Annual Plan, which arrays the resources available to the NTP and the compounds it has on test and proposes to put on test in the upcoming year, and the Annual Report on Carcinogens (mandated by P.L. 95-622), which contains a list of substances known or reasonably anticipated to be carcinogens to which a significant number of people living in the United States are exposed. NTP also has made several improvements in the toxicology and carcinogenesis bioassay reports it publishes, and it is working to speed publication of these reports. So that study information can be made available prior to completion of the full bioassay and its report, NTP is beginning to publish interim bioassay reports giving results of the pre-chronic testing phases. NTP maintains a computerized management status file for chemicals in various stages of testing, from which a listing of all chemicals and their test status can be produced. These lists are distributed quarterly to about 650 individuals outside the program who require information about the movement of chemicals through the NTP.

To disseminate information about NTP test results and program activities on a more frequent basis, NTP has developed a Technical Bulletin. These bulletins are sent to all who request, and currently about 3,500 names are on the mailing list. Notices of all major NTP activities, including the Board of Scientific Counselors meetings, nomination of chemicals for testing, selection of chemicals for testing, and meetings held to review the NTP Annual Plan are announced in the Federal Register. Transcripts of the open meetings held to receive comments on the annual plans are distributed widely. To increase the amount of information available to the program, NTP has arranged for the National Library of Medicine to provide a broad range of information support services, including use of on-line information services. NTP has assumed responsibility for supporting the Environmental Mutagen Information Center (EMIC) and the Environmental Teratology Information Center (ETIC), both at Oak Ridge National Laboratory, to collect, organize, and disseminate previously published information on chemicals tested for mutagenicity and teratogenicity.

Other Evidence Suggestive of Program Efficiency, Effectiveness, and Responsiveness

Because the NTP represented a new way of coordinating research throughout the Department when it was established, the HHS Secretary asked that the Office of Management and Budget (OMB) conduct a management review of the program in 1980. The OMB study team reported it found indications of initial success by NTP in moving toward each of its goals.(5) Specifically, the study team reported that progress has been made in expanding the number of tests, especially in the short-term testing area; in broadening the scope of the tests, especially in the long-term test area; and in developing agreement on protocol design. The study team also indicated that the long-term nature of the goals of the program and the newness of the NTP made it impossible to evaluate definitively the NTP on the basis of end results achieved during the short period of its existence.

For this reason, the OMB study team turned to an identification and assessment of process goals to gauge the potential of the present organization to meet its mission. The study team selected three broad process goals to assess the performance of the NTP: consensus building, guidance issuance, and operational responsiveness. In terms of tangible end results, the study team found that the special set of organizational arrangements known as the NTP has resulted in progress being made in the management of toxicological activities. Three indicators of this progress are: (1) development by NTP of a list of chemicals that have been reviewed thoroughly and selected for testing, (2) prevention of duplicative testing of chemicals by DHHS and other governmental agencies through the interaction encouraged by NTP, and (3) establishment of a single organization within DHHS to serve as the repository for chemical testing information, as well as a source of consultation on issues relating to chemical toxicology. Based on its findings, the MB study team expressed its belief that the NTP offers the highest probability for success because of the experience it has gained and the relationships it has developed. The Assistant Secretary for Health subsequently recommended that the Secretary establish the NTP as the permanent mechanism for coordinating DHHS toxicological research and testing. The Secretary has approved this recommendation.

Other evidence provides indirect measures of the efficiency, effectiveness, and responsiveness of the NTP program. One type of evidence relates to the approval of NTP technical reports with respect to their scientific quality and relevance. In early 1979, the NTP took over direction of the carcinogenesis testing program, which is now called the bioassay program.

Since that time, release of 42 peer-reviewed technical bioassay reports has been announced in the Federal Register. Since June 1980, when the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors began operation, an additional 32 reports have been peer-reviewed and approved and are in various stages of preparation for publication. Only three reports were returned by the Subcommittee for clarification and rewriting, and these were given approval once the technical revisions were made.

One of the central functions of the NTP is to serve as a focus of coordination for toxicology test development and testing among the relevant health research and health regulatory agencies. NTP's effectiveness in carrying out this function is demonstrated by its successful development of coordinated annual plans that array the resources available to the NTP and the compounds it has on test and proposes to put on test in the upcoming year. Through the unique combination of research and regulatory agencies working together to develop a program of action, the NTP is providing a framework within which these agencies can achieve a complementary approach to solving environmental problems and protecting the public health.

NTP's effectiveness in serving as the focus of coordination also is demonstrated by its successful development of a chemical nomination and selection process that enables the NTP to take into account the needs of its various research and regulatory agencies. For example, in FY 1979 the Occupational Safety and Health Administration submitted for NTP's consideration for bioassay testing a list of more than 60 compounds, of which more than 50 now are in various stages of analysis; 16 of the first 17 substances the Consumer Product Safety Commission nominated for testing are being tested by NTP. NTP's prechronic tests also are more useful than the bioassay alone for risk assessment, which is of critical concern to the regulatory, as well as the research, agencies. As another example, out of 24 suspect chemicals selected by NTP for testing, 50 percent were demonstrated to be carcinogenic in animals under conditions of the tests, 45 percent were considered negative, and 5 percent were equivocal but not proven carcinogenic in testing completed in FY 1980. Thus, through the coordinated efforts of the participating research and regulatory agencies, the NTP has been able to supply the type of information these agencies need to select appropriate strategies for dealing with environmental problems and public health threats. This cooperation among the NTP agencies highlights the progress and potential of the program.

Still another measure of NTP's effectiveness has been its ability to meet two short-term goals that had to be achieved in the early years of the program. The first of these was to strengthen cooperation between NCI and NIEHS in the development and testing of test methods. Because these two Institutes provided 87 percent of the funding for NTP, it was critical that their efforts be well integrated. The second short-term goal was to open the planning and operation of the NTP to scrutiny and comment by nongovernmental groups, in order to strengthen the program and the program's acceptance by affected parties. As previously mentioned, the first goal has been realized and acknowledged through the Secretary's approval of the administrative transfer of the NCI carcinogenesis bioassay program to NIEHS. The Secretary approved this transfer on July 14, 1981, and these two components are now being managed as an integrated whole.

With regard to opening NTP's planning and operational process, NTP provides greater access to the program by research and regulatory agencies through the Executive Committee and the chemical selection process. It also provides the opportunity for public comment on nominated chemicals through Federal Register announcements. It publishes the NTP Annual Plan, the Annual Report on Carcinogens, and the NTP Technical Bulletin, and solicits public comment on each. It holds open meetings annually to receive comments, criticisms, and suggestions on all aspects of the program. Finally, the NTP provides for broad review of the expanded draft bioassay reports and for comments on them, in order to maintain high scientific standards and to make them more applicable to regulatory needs. Thus, NTP has progressed significantly toward strengthening involvement in the acceptance of the program.

Another measure of the NTP's effectiveness relates to the public health problems it has been able to address. The NTP has played an active advisory role in the Love Canal problem; and it has completed, or is continuing, its testing of approximately 70 of the almost 300 chemicals found in that dump site. NTP staff have also taken an active role in interagency groups charged with evaluation the health effects of Agent Orange; and NTP scientists have completed reproductive assessment studies using male mice exposed to components of Agent Orange, which revealed no reproductive effects in offspring sired by those mice. NTP recently completed some of its studies on the chronic toxicity of orally ingested asbestos and on the toxicity of polybrominated biphenyls (PBBs), both of which are current environmental health problems in the United States. Under the test conditions, orally ingested asbestos was found not to be carcinogenic to hamsters, while the PBBs tested were found to be carcinogenic to rats and mice. Scientists from all the agencies of the NTP currently are carrying out a special testing initiative involving integrated testing of 16 dyes based on benzidine and benzidine congeners for mutagenicity, chemical disposition, and carcinogenicity. This testing is expected to provide results that may be applicable to other dyes in these classes. A recently completed NTP carcinogenesis study of the most widely used phthalate plasticizer has demonstrated that the compound is carcinogenic in rats and mice. Because this finding has heightened concern about the carcinogenic effects of other members of this chemical class, the NTP has developed a testing initiative on the phthalate esters.

Studies Now Under Way That Will Assess Program Performance

Although the program is still young, one of its important elements is its ongoing self-evaluation to determine if the program is meeting its objectives and is being effective in carrying out its programs, as well as in using the resources of the Department. This evaluation process consists of five basic elements:

- The tracking of the status of the implementation plan;
- Development of the annual plan, which details the number of chemicals to be tested, the test procedures to be followed, and a schedule for the tests;

- Oversight of the implementation of the annual plan by the Executive Committee;
- Oversight of the scientific quality of the program by the Board of Scientific Counselors; and
- Development of an approved annual report that specifies the extent to which the goals of the annual plan have been achieved.

Proposed Studies That Will Assess Program Performance

When the HHS Assistant Secretary for Health recommended to the Secretary that he establish the NTP as the permanent mechanism for coordinating the Department's toxicological research and testing activities, he also recommended that a management review be scheduled after two years. This review will assess program performance two years after the experimental phase of the program design was ended.

Major Issues or Problems Cited by Organizations Within the Administration, Congressional Committees and Organizations (GAO, CBO, CRS, OTA), and Interest Groups

The creation of the National Toxicology Program has been applauded as a positive step toward better integrating existing toxicology testing resources. To date, no Congressional committee or Executive agency (such as OMB) has undertaken a review that criticizes the program.

Of interest, however, are the July 1981 oversight hearing mentioned above and the June 1981 report of the Office of Technology Assessment (OTA), "Assessment of Technologies for Determining Cancer Risks from the Environment."(6) The OTA report concludes with 11 options, 2 of which relate directly to the NTP:

- Option 5: Encourage NTP to pursue the development of tests to replace the long-term carcinogenicity bioassay in small mammals.

  Under this option, OTA stated that NTP has improved the management of the Government bioassay program; however, no improvements are expected in two aspects of the tests: they are expensive and they require a great length of time. For this reason, OTA suggested that Congress might encourage short-term test development and validation, and might consider additional funding for the programs. OTA said that a potential disadvantage of relying on NTP for guiding and directing this research and development effort is that NTP has many other responsibilities. NTP also is responsible for the management of large animal test programs. As a part of a multipurpose program, short-term test development has to compete for resources with other parts of the NTP.

  With regard to this potential problem, it should be noted that the NTP has determined to concentrate on stabilizing the number of compounds it puts on test in each of its activities, so that the potential problem of different parts of its program having to compete for resources should not arise. In addition, as the private sector assumes more responsibility for testing under TSCA, the NTP expects to be able to devote more of its resources and attention to the critical task of test method development and validation. NTP already has been able to increase the allocation of funds for test methods development and validation from 14 percent of its budget in FY 1980 to 22 percent in FY 1982.

- Option 7: Expand support of the National Toxicology Program.

  OTA stated that "NTP has made a promising start at managing DHHS's short-term testing and animal toxicology program and has been successful in organizing expert advice for its programs. It has assembled a board of nongovernment scientists to advise the overall program, a panel of regulatory agency representatives to aid in selecting chemicals for animal carcinogenicity bioassay, and, most recently, a panel of nongovernmental experts to review the results of animal tests for carcinogenicity. Each of these efforts increases the sources of advice for NTP, and assures NTP higher visibility."

  The OTA report continued, "Arguments for encouraging and expanding NTP center on its promising start, its attention to immediate testing needs through the bioassay program, and from the possibility of future payoffs from new test development."

Other Major Barriers and Issues Relating to Program Performance

During its first three years of operation, the NTP has faced a number of difficult issues that have affected program performance. With the transfer of the NCI carcinogenesis bioassay program to NIEHS, however, major issues relating to managerial control and funding have been largely resolved. The Secretary's approval of the recommendation by the Assistant Secretary for Health that the NTP be established as the permanent mechanism for coordinating the DHHS toxicological research and testing activities has settled questions relating to the permanence of the organizational structure.

This, combined with the fact that approximately 87 percent of NTP's resources are now consolidated in the NIEHS, will permit NTP to undertake more detailed long-range program planning. Still remaining is the issue of staffing.

The only significant staff increases provided the NTP have been in the carcinogenicity testing area. Yet much of this increase is required to meet the commitment to shift from use of a prime contractor to Government management of many of the NCI's former testing contracts. As a result, NTP is not adequately staffed to permit optimal design, planning, and management of the total NTP. Resolution of this issue will depend upon Departmental, Administrative, and Congressional actions.

In spite of the constraints imposed on the program, the NTP has made significant progress in integrating the DHHS activities in toxicology research and testing and in developing stronger links between toxicology research and the needs of the regulatory agençies. Specific accomplishments include NTP's development of coordinated research and testing programs; structural supports to facilitate consolidation of NTP efforts; integrated research and testing activities, featuring expanded test protocols, and new and improved test methods; and enhanced information dissemination.

Documentation

1) P.L. 95-622, "Community Mental Health Centers Act Amendments," November 9, 1978.

2) House Report 96-244, p. 30, June 7, 1979.

3) House Report 96-1244, p. 51, August 21, 1980.

4) NIEHS staff notes from the House Committee on Science and Technology, Subcommittee on Investigations and Oversight Hearings on the National Toxicology Program, July 15-16, 1981. (Hearing report not yet printed.)

5) Memorandum to the HHS Secretary from the Assistant Secretary for Management and Budget on "National Toxicology Program Evaluation," December 11, 1980.

6) Report to the Congress by the Office of Technology Assessment on "Assessment of Technologies for Determining Cancer Risks from the Environment," June 1981.

NATIONAL EYE INSTITUTE

Director's Overview

Significance of the Health Problem

Over 10 million people in the United States--one in every twenty--are affected by visual impairments which are not amenable to further improvement with corrective lenses. Of these, 1.5 million have such severe impairment that they are unable to read ordinary newsprint, even with glasses. Of those severely impaired, approximately 500,000 are legally blind.

Each year, over 3.7 million new cases of eye disorders are diagnosed, and approximately two million eye injuries occur. Eye conditions necessitate over 31 million visits for professional care each year. Approximately 800,000 people are discharged from hospitals each year with an eye disease or disorder as a recorded diagnosis.

Eye disorders are outranked only by arthritis and cardiovascular diseases as a leading cause of limited activity among persons 65 years of age and older. Approximately 1.7 million people are limited in their daily activities because of visual impairment.

The total cost of visual disorders and blindness to our Nation is now estimated at approximately $7 billion per year in direct health care costs and in indirect costs associated with lost income and disability payments.

Most blindness and visual disability in the United States is caused by chronic disorders of the retina, examples of which are diabetic retinopathy, senile macular degeneration, and retinitis pigmentosa. No means of prevention or cure exist for most retinal diseases, although impressive progress has been made in preventing blindness from diabetic retinopathy thanks to research supported by the National Eye Institute (NEI). Other leading visual problems are cataract, glaucoma, uveitis, corneal infections and dystrophies, strabismus, and amblyopia. Although treatments are available for some of these conditions, most leave much to be desired, and means of prevention are generally lacking. Although eye disorders are seldom fatal, they may cause a lifetime of hardship and financial burden, seriously restrict the daily activities of millions of adults, and rob a large portion of our elderly of the rewards of their retirement years.

Research Program Strategy

Because much still needs to be learned about the basic structure and function of the visual system in health and disease, about 48 percent of the National Eye Institute's current and projected budgets supports the development of basic knowledge. And, because NEI is committed to the philosophy that the best way to gain knowledge of basic mechanisms is through support of the most meritorious research proposals generated by individual investigators, about 85 percent of the NEI research grants budget supports regular research project grants (R01s).

The basis for NEI's research program strategy is contained in the detailed and comprehensive document Vision Research--A National Plan, the latest edition of which covers the years 1978-1982. This plan, prepared under the aegis of the National Advisory Eye Council, is currently being updated for the years 1983-1987. In the new plan, for each of NEI's five major programs, research goals and objectives are redefined, recent accomplishments documented and assessed, current vision research support by NEI and other organizations analyzed, current research needs and opportunities discussed, priorities for future program development highlighted, and resource requirements estimated.

The national plan is designed as a guide to the research community in the development of research grant proposals, to the NEI staff in carrying out various program initiatives such as the planning and organization of scientific workshops and the drafting of Requests for Applications, and to the National Advisory Eye Council in determining the program relevance of individual grant proposals and in overseeing the entire NEI program. By consolidating the views of the best minds in the vision scientific community concerning the best opportunities for fruitful research over the next five years and the appropriate balance of support among the several areas of vision research during that period, the plan is aimed at making maximal and optimal use of NEI's fiscal and manpower resources and at hastening fulfillment of the Institute's mission.

In addition to identifying specific basic research approaches which are likely to lead to progress against leading causes of blindness, the new NEI plan will highlight opportunities for clinical research, including clinical trials of promising new diagnostic and therapeutic methods. Clinical trials are becoming an increasingly important part of the NEI's research strategy. The NEI is now supporting 25 clinical trials, two of which are large-scale, multicenter projects funded by contracts and the rest are either single center or multicenter trials supported by individual research project grants.

However, a shortage of trained clinical investigators may limit further development in this area. Therefore, the NEI has taken the following steps to help remedy this situation: (1) reducing the minimum time required for research training under NRSAs from two years to one; (2) a program for short-term research training for medical students, particularly during the summer; (3) a "clinic" on the NIH grants process at the annual meeting of the American Academy of Ophthalmology; (4) an annual postgraduate course in clinical research methodology; (5) presentations on research opportunities to university departments of ophthalmology not presently receiving NEI support; and (6) a new research grant mechanism, a small grants program for pilot projects, including feasibility studies of innovative or high-risk research and the testing of new techniques.

The new NEI construction grant program, authorized by the Congress in 1978, received its first appropriation of $3 million in FY 1980. The first awards under this program are expected to be made in January 1982.

Relevance of Program Strategy to Broader Health Objectives

The goals of the National Eye Institute are to improve the prevention, diagnosis, and treatment of visual disorders, thereby alleviating human suffering and reducing the expense of medical care and other social and economic costs. In considering the potential relevance of the above research strategy to achieving these goals, it may be useful to review some of the accomplishments of the past decade to see how effective this strategy has been.

Cataract extraction has become one of the safest and most successful of all major surgical operations. New antiviral and antibiotic drugs have revolutionized the treatment of ocular infections. Corneal transplantation has become highly successful because of improvements in tissue preservation and operating procedures and better assessment of prospective tissue donors and recipients. The course of diabetic retinopathy, virtually hopeless just a few years ago, is now being successfully controlled by two therapies, photocoagulation and vitrectomy. Although some of these advances have required the development and use of expensive medical technology, the savings in reduced hospital days and days lost from work, not to mention alleviation of pain, disability, and anxiety, have more than offset this added expense.

FY 1981--Examples of Areas of Research Holding Great Promise for Progress and/or Major Advances and Recent Accomplishments

- Early Treatment Diabetic Retinopathy Study. This new collaborative clinical trial is based upon the results of an earlier trial, the Diabetic Retinopathy Study, which showed that xenon arc or argon laser photocoagulation can sharply reduce the risk of blindness from advanced diabetic retinopathy. In the new study, investigators are trying to determine whether treatment earlier in the course of diabetic retinopathy, either by argon laser photocoagulation alone, aspirin alone, or the two treatments in combination, can delay or prevent progression of early diabetic retinopathy to high risk stages. The new study is also assessing the effectiveness of these treatments in preserving or improving vision in diabetics with macular edema, swelling of that part of the retina responsible for sharp central vision.

- Immunology and Immunotherapy of Uveitis. Uveitis is a general term for inflammatory diseases of the uvea, the eye's middle coat, and is responsible for 10 percent of all visual impairment in the United States. It has recently been discovered that some cases of uveitis may be triggered by exposure of the immune system to a retinal protein called rhodopsin kinase. This enzyme is present in all normal eyes as a component of the light-sensing cells of the retina. This discovery lends weight to the longstanding suspicion that many cases of uveitis are autoimmune in origin. With the benefit of this information NEI intramural investigators have been able to develop an animal model of uveitis and test various drugs as treatments. They have discovered that cyclosporin A, a drug used to control tissue graft rejection, can prevent the development of autoimmune uveitis in rats injected with rhodopsin kinase. Evaluation of this drug in human uveitis is now underway.

- Research Aimed at Improved Control of Recurrent Herpes Keratitis. Much of the damage to the eye caused by herpes virus is due to the chronic recurrent pattern of this infection. An important recent discovery is that latent herpetic reservoirs in deep-seated neuronal tissues in the brain, neck, and spinal column are the source of recurrent viral infections. Such latent neuronal viruses are beyond the reach of topical drugs, but recent studies indicate that systemically administered medications have some effect on reducing their level. Studies have also indicated that some herpes strains may be more prone to cause recurrent and severe disease than others. This suggests that biologic derivatives of mild herpes strains or recombinant DNA altered strains in the form of a vaccine may be used to block recurrent herpes infections. If the biology of latent and recurrent ocular herpes can be better understood, this could also lead to elimination of recurrent cold sores and venereal herpes.

- Clinical Trials of the Role of Aldose Reductase Inhibitors in the Prevention of Diabetic Complications. The discovery that an enzyme, aldose reductase, initiates the formation of sugar cataracts (those associated with diabetes) has led to findings indicating that the enzyme may also be involved in other diabetic complications. Potent chemicals have been found that inhibit aldose reductase activity and block the formation of diabetic cataracts in animals. Aldose reductase inhibitors are now being tested clinically for their ability to prevent lens swelling, a cause of transient blurring of vision in diabetics, and loss of conductivity in peripheral nerves, another frequent complication of diabetes.

- Laser Treatment of Angle-Closure Glaucoma. Although surgery is highly effective in treating angle-closure glaucoma, which occurs acutely as a result of an anatomic predisposition to sudden blockage of the channels through which fluid normally flows out of the eye, scientists have sought simpler and noninvasive means of controlling this potentially serious condition. Recently, lasers have been used instead of conventional surgery to create a new fluid outflow channel. The results have been quite variable, but some investigators claim great success. It is hoped that through controlled clinical trials the most appropriate use of the laser in treating this condition may be determined.

- New Psychophysical Diagnostic Techniques. Psychophysics is concerned with gathering precise data to establish standards for measuring the way physical stimuli affect mental processes. In vision research, the recent development of methods for extending functional testing of vision from the qualitative to the quantitative level is highly significant. Such tests can be used to localize precisely the site of retinal anomalies, provide data which may lead to the prevention of visual disorders or to the optimization of remaining visual function in those who have lost vision, and aid in the acquisition of normative data against which data from people with eye disorders can be compared.

FY 1982 Program Changes

- Research Project Grants (R01, R23). Approximately 930 will be funded (630 noncompeting, 300 competing), an increase of 35 over FY 1981. At this level about 50 percent of approved grants can be paid. This will make it possible to provide adequate continued support for important areas of ongoing research such as those highlighted for FY 1981 and to undertake the following initiatives:

--Studies of the Role of the Protein Calmodulin in Retinal Cells. This vital protein plays a pivotal role in the regulation of many important cellular activities. In the retina a number of critical processes, including cyclic nucleotide metabolism and neurotransmission, may depend on the normal functioning of this protein. Studies now are aimed at determining if this protein may have a therapeutic effect on a form of retinal degeneration in dogs. Research in this field is expected to expand in FY 1982 and may ultimately lead to the biochemical treatment of some hereditary retinal degenerations.

--Culturing of Human Retinal Tissue. The *in vitro* study of human and animal retinal tissue is now possible. To an extent not previously possible, investigators will be able to study the renewal of retinal photoreceptor cells including the circadian nature of the shedding of photoreceptor discs. Thus it should be possible to measure biochemical and physiological processes in retinal tissue from normal humans and to assess the metabolic status of the retina in various inherited diseases such as retinitis pigmentosa.

--Further Application of Immunologic Techniques to Vision Research. Three workshops designed to stimulate discussion and collaboration among vision researchers and immunologists were held by the NEI in 1979-1980, one on "Immunogenetics and Transplantation Immunity," the second on "Autoimmune Phenomena and Ocular Disorders,"and the third on "Infection, Inflammation, and Allergy." As a result, a number of immunologists have been attracted to the vision field and the NEI is supporting several new grants in areas that respond to the recommendations of the workshop participants. This trend is expected to continue and expand in FY 1982.

--Continued Development of Glaucoma Medications. Continuing emphasis will be placed on refining the drugs currently used to maintain normal intraocular pressure in glaucoma patients and on defining the mechanisms of drug action at the cellular level. Results of ongoing clinical trials to determine optimal uses of carbonic anhydrase inhibitors and the long-term safety and efficacy of timolol will be accumulating and may indicate changes in how these drugs should be used in treating glaucoma. Through research, new drugs may be identified and tested for safety and efficacy and compared to existing ones. The objective is development of medications that are effectively delivered into the eye, require less frequent administration, and are relatively free of side effects.

--Basic Research on the Visual Sensorimotor System. Emphasis will shift from neuroanatomy and neurophysiology toward accelerated research in neurochemistry and pharmacology. As far as the latter is concerned, a beginning can be made in research on clinical applications, especially in the visual disorders associated with more generalized neurological disorders such as multiple sclerosis.

- Research Centers (P30, P50). Approximately 23 core awards, three more than in FY 1981, will be funded to promote sharing of central resources and interdisciplinary collaboration at institutions where an existing strong base of NEI support already exists. Two specialized clinical research center grants (noncompeting) will continue to be funded.

- Research Career Awards (K04, K07). About 38 awards, a decrease of 22 from FY 1981, will be made to foster the career development of new and established laboratory and clinical research scientists with outstanding potential for careers in vision research.

- Cooperative Clinical Research Grants (R10). About 29 awards, two less than in FY 1981, will be made to permit continuation of ongoing clinical trials.

- Clinical Trial Development Grants. Funds will provide for about eight of these new awards, the specific purpose of which would be to support the development of a detailed protocol and manual of procedures for high priority clinical trials of new treatments or diagnostic procedures.

- Research Training (F32, T32). Approximately 61 full-time equivalent (FTE) positions will be supported under individual fellowships, and approximately 128 FTEs under institutional fellowships, in such high priority areas as ocular immunology, genetics, pharmacology, epidemiology, biostatistics, physiology, biochemistry, developmental biology, psychophysics, physiological optics, and experimental and clinical pathology. This level of support would amount to 11 fewer trainees than in FY 1981, and about 89 fewer than in FY 1981.

- Research Contracts (N01). An estimated 54 contracts would be funded to support two ongoing multicenter clinical trials, the Diabetic Retinopathy Vitrectomy Study and the Early Treatment Diabetic Retinopathy Study.

- In FY 1982 plans will be underway for the NEI supported Visual Acuity Impairment Survey (VAIS). The VAIS is an epidemiological study of the prevalence of central distance visual acuity impairment in the United States and the eye diseases responsible for the impairment. The survey will be carried out in FY 1983 on samples of the adult population (age 25 and older) of 15 large metropolitan areas. (A pilot survey in three geographic areas will be made in 1981-82). In addition to an ophthalmologic examination, the study also involves a general health interview survey which will describe the population in which the visually impaired persons are found, by age, sex, and other demographic characteristics. Examinations will also be done on persons without impairment to provide unbiased, population-based controls of the diseases that are major causes of visual acuity impairment.

- Intramural Research. Present activities will be sustained and allowance made for initial occupancy of the Ambulatory Care Research Facility. A new intramural research program will be established, the Laboratory of Molecular and Developmental Biology. The goal of this laboratory, which will perform basic research on gene expression and molecular interactions in the visual system, is to understand the genetic and molecular foundations of the developing and mature eye. Certain diseases of the eye, such as cataract, will be examined in molecular terms. A genetic and molecular dissection of the visual system holds great promise for making important advances in understanding the normal eye as well as genetic and metabolic diseases of the visual system.

- Direct Operations and Program Management. Additional funds are provided for a 4.8 percent pay raise.

- Construction. No additional money is provided for NEI's new program to construct vision research facilities.

FY 1983 Program Changes

- Research Project Grants. Approximately 1,002 grants could be funded, 294 of which would be competing renewals and 160, new awards. This would enable payment of 44 percent of approved applications, an award rate slightly below that for FY 1981, and make it possible to take advantage of many of the research opportunities that will be identified in the NEI's new national plan. Although these priorities have not yet been finally established, the following are a few of the major research needs and opportunities in each NEI program which will most likely be identified as program development priorities.

Retinal and Choroidal Diseases

--Further develop techniques to study the altered retinal blood flow in vascular diseases such as diabetic retinopathy.

--Study the metabolism of retinal capillary cells in freshly isolated specimens and in tissue culture.

--Apply new immunologic techniques to study of the cause and treatment of uveitis.

--Establish a multicenter clinical trial to compare the efficacy of enucleation compared with radiation in the treatment of choroidal melanoma.

--Pursue further the biochemical correction of hereditary eye diseases.

--Study the effects of toxic substances on the macula.

--Study the molecular mechanisms involved in normal photoreceptor renewal and their disruption in retinal degenerative disease.

--Study the biochemistry of the retinal pigment epithelium.

Corneal Diseases

--Determine the neuronal and viral factors contributing to herpetic latency.

--Investigate the use of monoclonal antibodies, programmed lymphocytes, and recombinant DNA techniques in manipulating the immune response to ocular herpes virus infections.

--Develop new therapeutic approaches for tear abnormalities, a leading cause of visual impairment and chronic discomfort among the elderly.

--Study the biological effects of existing and proposed medical and surgical procedures for the correction of refractive error.

--Further improve corneal preservation techniques.

Cataract

--Study lens cell division, fiber differentiation, and protein synthesis in tissue culture to understand the normal lens better.

--Use recombinant DNA and cell hybridization techniques to improve knowledge of genetic control of lens development.

--Determine cataract risk factors through case control and other epidemiologic studies.

--Study the natural history of senile cataract *in vivo*.

--Study the antioxidant defense mechanisms of the lens, particularly as they relate to light-induced mechanisms of cataract formation.

--Study the role of nutrition in human cataract formation.

--Study the biochemical effects on the lens of commonly used drugs known to cause cataract.

--Search for nonsurgical treatments of cataract.

Glaucoma

--Develop noninvasive techniques for studying aqueous humor inflow.

--Conduct studies of cellular anatomy, physiology, biochemistry, and pharmacology of the outflow pathways using isolated cells in intact tissue or in culture.

--Identify the site(s) of outflow obstruction in primary open-angle glaucoma.

--Explore the epidemiology of glaucoma, concentrating on possible risk factors and the basis for racial differences in disease incidence and severity.

--Develop new drugs that might have long-lasting or permanent effects on reducing aqueous outflow resistance.

--Develop means of preventing and treating glaucoma secondary to ocular injuries.

--Determine the link between underlying disease and the development of neovascularization in the eye's anterior chamber leading to secondary glaucoma.

Sensory and Motor Disorders of Vision

--Improve understanding of the neural basis for damage by and recovery from the effects of early visual deprivation such as amblyopia and strabismus.

--Improve techniques for assessing visual function in infants to improve early diagnosis and treatment.

--Further study neurotransmitters in the visual system, and especially seek to determine if gel peptides serve as transmitters.

--Use immunologic techniques to study the development and functioning of visual nervous system components.

--Conduct controlled clinical trials of treatments for amblyopia including possible new pharmacologic and surgical treatments.

--Further study the role of heredity, environment, diet, and disease in the development and progression of myopia and other refractive errors.

- Research Centers. Approximately 24 (six new) core grants would be awarded.

- Research Career Awards. Twenty-three noncompeting grants would be awarded.

- Cooperative Clinical Research Grants. Twenty-nine would be awarded, seven of them new.

- Clinical Trial Development Grants. Ten grants (all new) would be awarded, allowing an average of two clinical trials per program to be implemented of those recommended in the new plan.

- Research Training. Approximately 200 (53 new) FTEs would be supported, eleven more than 1982. This would be fewer trainees than NEI supported in FY 1980.

- Research Contracts. Funds are added to provide initial support of the Visual Acuity Impairment Survey.

- Intramural Research. Ten positions would be added: three for support of patient activities in the ACRF, two for sensorimotor research, and five for the new Laboratory of Molecular and Developmental Biology.

- Direct Operations and Program Management. Five positions would be added: one for administration of NEI's Construction Grant program, two to administer the Visual Acuity Impairment Survey, one to administer the Prospective Evaluation of Radial Keratotomy study, and one to administer the Early Treatment Diabetic Retinopathy Study.

Potential Impact of Program Changes on Three-Year Period (1983-1985)

The NIH three-year planning period coincides with the initial three years of the forthcoming national five-year vision research plan. A selection of research areas expected to be emphasized in the new plan is listed under FY 1983 Program Changes; however, these and the other areas of research highlighted in the national plan are expected to constitute NEI's program priorities for at least the duration of the three-year NIH planning period.

With the opening of the Ambulatory Care Research Facility (ACRF), NEI's intramural program will for the first time have the physical resources necessary for taking full advantage of the unique NIH campus research environment. The new NEI Laboratory of Molecular Biology is expected to be fully operational by the beginning of the planning period and will add a major new dimension to the existing components of NEI's basic and clinical research program.

In both intramural and extramural programs the following general cross-cutting categories of research will be active during the planning period:

- Prevention. Currently over 25 percent of NEI's budget is devoted to projects expected to gain information relevant to preventing eye diseases and disorders and blindness. This emphasis is expected to continue and possibly increase as funds become available during the planning period.

- Aging. Although eye disorders affect people of all ages, their primary impact is on the elderly. Currently, approximately 10 percent of NEI grants support research directly related to problems of the aging. Particular attention is paid to research aimed at the prevention of cataract and macular degeneration, two of the most common aging-related eye disorders.

- Diabetes. NEI-supported research has already made major contributions to the general field of diabetes research and has had a significant impact on the prevention and reversal of visual impairment from this disease. In the past, emphasis has been placed on clinical research. This emphasis will continue, but in the planning period increased advantage will be taken of opportunities for fundamental studies on the etiology and pathogenesis of diabetic changes in ocular tissues.

- Neurobiology. A major portion of NEI's program is devoted to basic neurobiological investigations in which the eye is the model system used. NEI-supported investigators, both intramural and extramural, are in the forefront of research in this field. Neurobiological research relevant to the NEI mission will continue during the planning period with increasing emphasis on translating results of such studies into clinical applications.

- Nutrition. NEI currently devotes $3.5 million to research on nutritional aspects of vision. Although nutritional deficiency is not a major cause of visual problems in the United States, it is a leading cause of blindness worldwide. The NEI has taken a modest but significant leadership role under the auspices of the World Health Organization's Prevention of Blindness Programme in fostering research in developing nations on the prevention of nutritional blindness. NEI collaboration with the National Institute of Nutrition of India in the development of a vitamin A research center is expected to be fully underway during the planning period.

- Epidemiology. The new plan will identify several opportunities for epidemiologic research, especially on cataract and glaucoma. The NEI will make special efforts to encourage well-designed studies aimed at identifying risk factors for these and other ocular disorders.

MEMORANDUM

NEI

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Eye Institute

DATE: JAN 30 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I noted with interest your strong commitment to the Institute's planning and evaluation function. The comprehensive plan developed for vision research, as well as the updates of that plan, have served your Institute well. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

DS Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

Entering its twelfth year of operation, the NEI has undergone steady program expansion in terms of funding, increased diversification in the use of program mechanisms, and coverage of substantive research areas. Although the qualitative development of the Institute has been excellent, problems still remain in obtaining a staffing level adequate enough for the required depth of coverage.

Impact of Stabilization in FY 1982

- The Institute will continue to allocate approximately 90 percent of its extramural funding to the support of individual research project grants.

- The number of core grants and centers supported will decrease slightly from 1979 and 1980 levels.

- Significant decreases will occur in the Research Career Development Award Program.

- Support for research training will decline for both individual and institutional awards at a time when the need for trained clinical investigators in vision research continues to increase.

- The number of research and development contracts supported will remain the same from 1980 through the 1983 current level. These contracts support the two ongoing multicenter clinical trials, the Diabetic Retinopathy Vitrectomy Study and the Early Treatment Diabetic Retinopathy Study and without adequate allowances for increased costs in 1983, negotiations with participating clinics will be difficult, creating the possibility that some centers will drop out of the studies. This could prolong the time for recruitment of an adequate patient population and possibly compromise the scientific quality of data collection and analysis and follow-up of patients. Also, it will not be possible to fund the full-scale national Visual Acuity Impairment Survey (VAIS) in 1983 without program increases.

- No significant program expansion will occur in intramural research in 1982; present activities will be sustained and allowance has been made for initial occupancy of the Ambulatory Care Research Facility.

- The NEI indicated that stabilization might result in some imbalances in intramural research and centers. Once final 1982 budget levels are established, it may be necessary to consider some type of reprogramming to address these imbalances.

Program Trends

- Research on the visual system is at the leading edge of current investigations in neurobiology. Among the advantages of this system are that the input and output can be measured with great precision and much of its morphology, physiology, and pathology can be evaluated in vivo. NEI's interest in this field includes studies of neurotransmitters in the visual system and studies to improve the neural basis for damage by and recovery from the effects of early visual deprivation. The extent to which the other Institutes provide support in the field of neurobiology needs to be examined. Please consider how this may be addressed at the program review sessions to be held in the spring/fall months.

- The visual system is increasingly being studied by cell biologists. Investigators are recognizing the unique properties of the lens to pursue studies of cell metabolism and membrane biochemistry.

- Immunologists are demonstrating increased interest in studying the visual system, particularly in applying new immunologic techniques to investigating the cause and treatment of uveitis.

- The process for the awarding of funds under the Vision Research Construction Program is on schedule. Applications will be reviewed in the spring and awards made in early 1982.

Issues

- The Institute perceives a need for 36 additional positions as a minimal requirement with which to carry out its full range of responsibilities. Twenty-five would be assigned to the intramural program, seven for direct operations, and four for program management.

- Inadequate numbers of trained clinical research investigators to carry out clinical trials and other forms of clinical research continues to be a major problem. The incentives for clinicians to enter into research training are poor due to the low stipend level and the payback requirement. To deal with this shortage, the NEI proposes to establish within the NRSA program a program for short-term research training for medical students, particularly during the summer, and to provide a special stipend for clinical investigators; to initiate a small program of pilot study grants to allow collection of preliminary data required for the development of a clinical research protocol; to initiate a clinical trial development grant as a one-year, one-time award which would provide sufficient funding for the development of a research protocol and manual of procedures. The NEI also plans to develop and distribute information on the support mechanisms available for clinical research training.

Action Items

Information is required concerning the extent to which patient care provided in the course of conducting extramural clinical trials is paid for by NIH funds. Dr. Robert Gordon, Special Assistant to the Director, will collect this information for all the BIDs with the assistance of the NIH Clinical Trials Committee.

A display is needed, showing over time the number of principal investigators (PIs) on research grants that are M.D.s and those who are Ph.D.s. Since it would be useful to see this data for each BID, I have asked Dr. Rhode, Chief, Program Analysis Branch, to provide this information.

Staffing Needs

Statement of Issue

The National Eye Institute still requires a minimal number of positions with which to carry out its responsibilities as a fully functioning NIH Institute. Although the NEI is now entering its twelfth year of operation, it has still not yet obtained a staffing level commensurate with its legislative mandate or sufficient to allow it to take advantage of some of the more outstanding opportunities that exist in its field.

Discussion of Issue

NEI strives only to be the smallest fully functioning Institute at NIH with an intramural program. It has neither the need nor the desire to be larger than its sister Institutes, but it does require that critical mass essential for participation in the full range of activities that these other organizations have. Specifically, positions are needed for the following:

- Adequate statistical and administrative monitoring of clinical trials.
- Intramural research training, particularly the training of clinical fellows.
- Follow-up of new research leads in the intramural program.
- Taking advantage of unique opportunities for international research.
- Administrative and scientific monitoring of research grants and programming of grants in high priority areas.
- Administration and scientific oversight of the intramural program.
- Indepth timely synthesis and analysis of program data for management use.
- Transfer of vision research knowledge to health practitioners and the public.
- Program planning and evaluation, particularly the evaluation of the effectiveness of implementation of the five-year NEI Plan.
- Dissemination of information concerning NEI program accomplishments and health educational materials.

Alternatives and/or Suggested Position

To carry out these activities, the National Eye Institute requests that an additional 36 positions be added to its base. Of these, 25 would be slated for the intramural program, seven for direct operations, and four for program management.

Clinical Research Investigators

Statement of Issue

Although numerous opportunities exist in vision research for important clinical trials and other forms of clinical research, there are inadequate numbers of trained clinical research investigators to carry them out. Although a shortage of trained clinical investigators is a problem not unique to vision research, the NEI has a few proposals for addressing this situation which may be applicable in other fields of biomedical research.

Discussion of Issue

With a few notable exceptions such as the cooperative retrolental fibroplasia study in the early 1950s, clinical research in ophthalmology has largely consisted of observational studies. Well-designed, scientifically sound clinical and epidemiological research has been a priority of the National Eye Institute from its beginning. The Diabetic Retinopathy Study, Diabetic Retinopathy Vitrectomy Study, Early Treatment Diabetic Retinopathy Study, and Framingham Eye Study have been examples of NEI initiatives which have served as models for the design of several other clinical and epidemiological research projects, most of which have been investigator-initiated. The studies have had a side benefit of providing on-the-job training in clinical research for numerous clinicians. Even so, the manpower for additional clinical studies is quite limited, and the incentives for clinicians to enter into research training remain limited. The implications of this are serious, for whole areas of vision research are still without an adequate base of clinical investigation. A prime example is the neurosensory field where an adequate study of the treatment of amblyopia and strabismus, significant causes of visual impairment among children, has yet to be designed.

Alternatives and/or Suggested Position

The NEI is prepared to take a number of steps to encourage the training of clinical investigators and the further development of clinical research. One proposal is to establish within the NEI NRSA program a program for short-term research training for medical students, particularly during the summer, which would afford such individuals very early in their careers an exposure to the scientific method and the opportunities for applying their clinical training to the solution of important diagnostic and therapeutic problems. Two disincentives for entering into clinical research training are the stipend level and the payback requirement. The NEI feels that legislative redress of these two problems will greatly enhance the entry of clinicians into research. The NEI also finds that even for trained investigators, the amount of work required to prepare an adequate protocol and manual of procedures for clinical studies can present a formidable barrier. To help remedy this situation, the NEI plans to institute a small program of pilot study grants to allow collection of preliminary data required for the development of a clinical research protocol. The NEI also proposes to initiate a clinical trial development grant, applications for which would be solicited in areas specified in its five-year plan. These grants are envisioned as one-year, one-time awards which would provide sufficient funding for the development of a research protocol and manual of procedures. When these documents are prepared, they would then be submitted to NIH for the usual peer review. As a further step to encourage both clinical research training and clinical research, the NEI plans to develop brochures and other printed materials which would explain in very simple language the array of support mechanisms available for this purpose. We find that the staffs of clinical departments are often not aware of what NEI resources are available to them and that they may be discouraged to some extent by the administrative jargon which has unfortunately too often attended our communications concerning research training opportunities.

PROGRAM PERFORMANCE SUMMARY

CATARACT RESEARCH

Program Description

The Problem Being Addressed

A cataract is an opacity or group of opacities in the crystalline lens of the eye which can interfere with the passage of light and cause visual impairment. The major types of cataract are senile, occurring in the elderly and accounting for 90 percent of all lens opacities; traumatic, resulting from accidents; drug-induced, from the toxic effects of drugs administered to treat ocular or systemic disorders; radiation, from the harmful effects of environmental or therapeutic radiation; congenital and/or genetic, occurring as birth defects or developmental disorders; and secondary cataract, a complication of other eye disorders or conditions--such as diabetes--or injuries.

Cataract is the second leading cause of blindess in the United States. Based on projections of available data, at least 42,000 persons in the United States are legally blind because of senile cataracts, and at least 4,600 become blind from cataracts each year. Congenital cataracts account for at least 14 percent of childhood blindess.

Cataract is also a major cause of visual impairment. Information from the National Health Interview Survey of the National Center for Health Statistics indicates that at least 400,000 people develop cataract each year. This disorder is responsible for 35 percent of existing visual impairment and 53 percent of new visual impairment with known etiologies. The prevalence of senile lens changes was found to be 42 percent for persons 52 to 64 years of age, 73 percent for those 65 to 74, and 91 percent for people 75 to 85.

As is true of almost all other eye diseases, the major impact of cataract is not death but physical limitation, psychological suffering, and financial burden. During cataract development, a process that may take 20 to 40 years, vision becomes progressively impaired.

The only effective way to treat cataract is surgery consisting of removal of the opaque lens. To lessen optical disability subsequent to cataract removal, the patient must be fitted with eyeglasses, contact lenses, or an intraocular plastic lens implant.

The magnitude of the problem of providing medical care for persons afflicted with senile cataract is apparent in data showing that in 1978 there were 3.5 million visits to office-based physicians because of cataract and 1.3 million visits because of aphakia (absence of the lens either because of cataract extraction, trauma, or congenital defect). In the same year, 900,000 office visits were due to cataract as a newly diagnosed condition. Also in 1978, about 400,000 cataract operations were performed in short-stay, non-Federal hospitals at a cost of approximately $1 billion. The added cost of implanting 100,000 intraocular lenses is about $50 million per year.

Statisticians estimate that development of a therapy that could delay the necessity for cataract surgery by 10 years would reduce the annual number of cataract operations by 45 percent. If one assumes hospital and surgical costs of $1,500 per cataract operation, the reduction in the total cost of cataract operations per year from about 400,000 to 220,000 would effect annual savings of at least $270 million. When this amount is added to the reduction in patient anxiety and suffering, it is clear that support for cataract research is an investment with a potentially high cost/benefit ratio. Certainly, in terms of physical disability, suffering, and financial burden, cataract constitutes a serious health problem, and therefore research into this disorder has been designated as an important component of the overall NEI program.

The NEI Cataract Program was established as one of the five NEI extramural programs shortly after the Institute was established. Subprograms within each of the five NEI programs were introduced in 1974 upon the recommendation of the National Advisory Eye Council's first Planning Subcommittee as a basis for more detailed program analysis and planning and as a means of focusing attention on the major aspects of each program, usually either a specific disease, etiologic entity, or scientific discipline. That program analysis and plan was published in the Council's 1975 planning report, Vision Research Program Planning; and a second more comprehensive evaluation and plan, Vision Research--A National Plan: 1978-1982, was published in 1977.

The present configuration of subprograms within the Cataract Program, shown below, was established in 1980 upon the recommendation of the Cataract Program planning panel appointed by the Council's third Planning Subcommittee.

- The Normal Lens
- Epidemiology of Cataract
- Senile Cataract
- Diabetic and Metabolic Cataract
- Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses
- Cataract Induced by Environmental and Toxic Effects
- Treatment of Cataract and Correction of Aphakia

The panel, consisting of cataract research experts in the extramural community, was charged with the task of reviewing the NEI program in the context of progress that had been made since publication of the previous planning report and developing a list of research priorities that reflect the scientific opportunities now available to meet the present needs of the Nation in cataract research.

The present panel not only renamed and reordered the previously established Cataract subprograms but added a new one: Epidemiology of Cataract. The panel's report, which will be published later this winter as a part of a third comprehensive five-year national vision research plan, discusses the general aims of epidemiologic research and the potential application of this discipline to solving problems associated with human cataract. Recent studies in the epidemiology of cataract have made important contributions, such as the establishment of a definite association between human cataract and diabetes. Although the existence of such an association had been a longstanding clinical impression, it could not be established through clinical studies of extracted cataracts, because of the self-selection of patients undergoing cataract surgery. It was only through NEI-funded epidemiological studies of populations that an association was shown to exist. Because of the success of these and other studies, and because knowledge of etiologic factors may lead to preventive measures, epidemiology has been determined to be so important that it warrants a separate subprogram classification. However, because this subprogram is new, we are not able to present data related to it before FY 1981.

In an effort to determine the causes of cataract and hasten the day when the condition can be medically treated or prevented, the National Eye Institute supports over 100 research projects on the normal lens and natural and experimental cataracts, seeking clues to the origin, mechanisms of formation, and improved treatment of this disease. The total amount of this support for FY 1981 is an estimated $9 million.

Legislative History of the Program

The Cataract Program operates under the following general authorities:

- General Institite Authority: 42 U.S.C. 289i; Section 451j, 425k, 453 of Title 4, part F of the Public Health Service Act, as amended. (Authority for establishment of NEI is quoted below.)
- General Research Authority: 42 U.S.C. 241; Section 301 of the Public Health Act, as amended.

NEI was established by Section 451 of the Public Health Service Act (42 U.S.C., 289;) as follows:

> The Secretary is authorized to establish in the Public Health Service an institute for the conduct and support of research for new treatment and cures and training relating to blinding eye diseases and visual disorders, including research and training in the special health problems and requirements of the blind and in basic and clinical sciences relating to the mechanism of the visual function and preservation of sight. The Secretary is also authorized to plan for research and training, especially against the main causes of blindness and loss of visual function.

There have been no legislative changes for NEI since its establishment.

Extramural Program Funding, Number of Grants, and Staffing

A table showing the recent budget history of the Cataract Program is presented on the following page.

In FY 1980, 14.2 man-years of effort were spent in cataract research in the NEI's intramural program. In that year cataract research accounted for 9.3 percent of the total extramural budget.

Program Objectives and Activities

It is considerably more difficult to evaluate programs that include both basic science and clinical research components than programs, for example, which are oriented toward health services or industrial production. In particular, it is difficult to establish program goals and objectives which are specific and measurable. Nonetheless, the NEI leadership and the Council believe that defining research program goals and objectives is an essential step in the evaluation and planning process. The objectives listed in this section were established by careful and comprehensive assessment of the cataract research needs of the Nation by the members of the Cataract Program planning panel.

Some of them are considered to be interim or short-range objectives, but even these establish a desired end toward which progress may be assessed by experts examining the state-of-the-art in the cataract field or, more objectively, by analyzing such health statistics trends as disease morbidity and the annual number of cataract extractions.

Program goals are:

- Find means of preventing or slowing cataract development in children and adults.
- Determine the causes and mechanisms of cataract formation.

Table 1
Cataract Program, Fiscal Years 1978-82
(Dollars in Thousands)

	1978		1979		1980		1981 1/		1982 2/	
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
Research Grants										
Research Project Grants (R01 & R23)	86	$5,937	103	$7,118	98	$7,314	91	$8,612	91	$9,795
Research Centers										
Center Core Grants (P30)	1	118	1	127	4	646	4	596	3	465
Specialized Centers (P50)	--	--	--	--	--	--	--	--	--	--
Other Research										
Research Career Development Awards (K04)	3	112	3	114	2	75	2	81	1	40
Academic Awards (K07)	--	--	--	--	--	--	--	--	--	--
Cooperative Clinical Research (R10)	--	--	--	--	1	207	1	210	1	193
Conferences (R13)	--	--	--	--	--	--	--	--	--	--
Scientific Evaluation	--	--	--	--	--	--	--	--	--	--
Research Training										
Individual (F32)	7	100	10	127	9	123	5	100	7	114
Institutional (T32)	4	168	5	191	5	250	3	154	2	130
Research Contracts	1	162	1	8	1	223	--	--	--	--
Intramural Research		717		807		947		1,063		1,178
Other		260		314		382		413		485
TOTAL	102	$7,574	123	$8,806	120	$10,167	106	$11,229	105	$12,400

1/ FY 1981 Continuing Resolution
2/ FY 1982 Revised President's Budget

- Understand the development, biochemistry, and biophysics of the normal lens.
- Evaluate the safety and efficacy of methods of cataract extraction.
- Evaluate new methods for correcting optical problems that follow cataract surgery.

Subprogram objectives are:

Normal Lens

- To understand the physiological, physicochemical, and biochemical mechanisms responsible for lens transparency.
- To understand the physical and chemical properties of the constituents of the normal lens.
- To understand the mechanisms that give rise to growth, cell differentiation, and differential gene expression in the lens.
- To understand the anatomical and mechanical factors involved in lens deformation.
- To understand the effects of cataractogenic agents (drugs and other external factors), ocular and systemic disorders, and aging on normal lens structures and function.

Epidemiology of Cataracts

- To assist in the development of an objective, reproducible, and standardized classification of type and severity of cataracts.
- To obtain valid and reliable data on the incidence and prevalence of cataracts.
- To determine the role of various environmental and genetic factors in cataract etiology.
- To evaluate diagnostic and therapeutic modalities in cataract management.
- To train investigators in the area of cataract epidemiology.

Senile Cataract

- To determine the cause(s) and pathogenesis of senile cataract, including its risk factors.
- To seek means to prevent, delay the progress of, or reverse the cataractous process.

Diabetic and Metabolic Cataract

- To understand and identify the factors involved in the development of diabetic and metabolic cataracts.
- To develop effective drugs which will slow or block the development of diabetic cataracts in man.
- To evaluate the safety and efficacy of drugs used in delaying or preventing diabetic cataracts.
- To establish cell lines in tissue culture from cataracts of different etiology.
- To elucidate further how diabetes can hasten the development of senile cataracts.
- To establish the role of nutrition in human senile cataract through epidemiological studies.
- To develop additional animal models and exploit existing methods for the study of diabetic and metabolic cataracts.

Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses

- To analyze cataracts on a population genetics basis.
- To understand better the mechanisms that lead to abnormal differentiation of the lens through biochemical and ultrastructural studies.
- To determine genetic versus environmental influences on the production of cataracts.
- To determine relationships to other ocular abnormalities and systemic diseases.
- To develop a reasonable classification of cataracts on the basis of genetic, biochemical, ultrastructural, and other parameters.
- To develop techniques for in vitro culture of human lens epithelial and fiber cells.

- To develop further animal models of genetic cataracts.
- To improve understanding of the mechanisms that lead to abnormalities of the lens zonule present at birth or occurring later in life.
- To understand better the biochemistry and ultrastructure of the lens zonule, which in turn may lead to understanding of the Marfan syndrome and various cardiovascular diseases.
- To develop animal models for these conditions.
- To develop treatment plans for the visual complications of dislocated lenses.

Cataract Induced by Environmental and Toxic Effects

- To identify and assess the biochemical and biophysical changes which take place in the lens as a result of insults from environmental radiation, as well as insults from chemicals and drugs.
- To protect the lens from such insults, thereby avoiding, or at least postponing significantly, the onset and development of cataract.

Treatment of Cataract and Correction of Aphakia

- To evaluate current techniques for cataract extraction and correction of aphakia and develop new approaches to these problems.
- To study the medical and preventive therapies of cataract.
- To determine the influence of aphakia on visual development in infants and children and to devise therapies.
- To establish standards and guidelines for toxicological studies of intraocular lens materials.

Assessment of Progress Toward Objectives

NEI extramural and evaluation staff, initial review group members, and ad hoc panels of expert scientists assess research accomplishments and progress in the cataract field through:

- The number and quality of scientific papers and monographs published by grantees in refereed journals.
- Analysis of the influence of these publications on the field of cataract research, e.g., citation analysis, bibliometrics.
- Evidence of accomplishments as described in progress reports on research grants

- The number and quality of presentations and lectures at scientific meetings and symposia.
- Data showing the progress that has been made in funding areas of research designated as priority in the NEI national plan.
- Indications from visual impairment surveys of trends in the incidence and prevalence of cataract.
- Data from ongoing national medical and hospital care surveys showing the burden of cataract on the health care system.

Summary of Current Program Activity

The dimensions of the NEI Cataract program in FY 1980 are outlined in Table 2 below, showing the number of research project grants (R01's) awarded in each subprogram. Only research project grants are shown because other support mechanisms in this program are either too few in number or do not lend themselves to such an analysis (see Table 1 above). Most work thus far on the Epidemiology of Cataract has taken place in the NEI Office of Biometry and Epidemiology. Although zero extramural activity is shown in this new subprogram, we hope that extramural scientists will be encouraged by the investigations performed at the NEI and respond to the needs and opportunities related to epidemiological research identified in the new planning report.

Table 2

Cataract Program, FY 1980
(Dollars in Thousands)

Subprogram title	No. of R01 grants	Total costs
The Normal Lens	35	$2,615
Epidemiology of Cataract	0	0
Senile Cataract	24	1,816
Diabetic and Metabolic Cataract	15	1,162
Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses	10	726
Cataract Induced by Environmental and Toxic Effects	7	509
Treatment of Cataract and Correction of Aphakia	6	436
Total	97	$7,264

Cataract research has evolved along three main paths: basic research into mechanisms of lens transparency or opacification, clinical and epidemiologic research into patterns of cataract formation in humans, and research aimed at improving techniques of cataract extraction and correction of resultant aphakia.

The previous table makes clear that much of the research being brought to bear on the problem of cataract consists of studies of the normal lens. Study of all aspects of the normal lens is of fundamental importance for understanding cataract because a variety of changes in normal structure and function have been linked to cataract development. The NEI funds studies that investigate such different lens phenomena as hydration, gene analysis, lens transport processes, protein aggregation, phase separation of protein-water mixture, epithelial cell hyperplasia, cell division, fiber cell differentiation, and the composition, distribution, and metabolism of lens proteins, carbohydrates, and lipids--all of which have been implicated in cataract formation. A major effort to study the cell biology, molecular biology, and biophysical properties of the lens has been undertaken. In particular, the role of lens proteins in the loss of lens transparency has received considerable attention.

Epidemiology, the subject of the second subprogram, is a cross-cutting area that is related to all cataract research. Laboratory research may provide etiologic clues to cataracts which can be tested by epidemiologic studies. Research into risk factors relating to cataractogenesis and classification and measurement of cataracts is important. Clinical advances in diagnostic and therapeutic techniques are also of major interest because they can help evaluate patient management. Unfortunately, there are very few ongoing projects in cataract epidemiology. In the United States most of the work in this area has and is being conducted by staff of the NEI's Office of Biometry and Epidemiology. Efforts are under way to increase epidemiological research in eye disorders generally.

Research on senile cataract has been greatly promoted by advances in cell biology and technological developments in the laboratory. The establishment of a nationwide Cooperative Cataract Research Group has also served to promote collaborative lens research and facilitate studies on the human lens. Ongoing investigations include study of the natural history of the cataractous process and of risk factors, the plasma membrane of normal and cataractous human lens fiber cells, the light-scattering entities of the cataractous lens, the antioxidant defense mechanisms of the lens, and the influence of environmental factors on cataractogenesis.

An understanding of the nature of diabetic cataracts is evolving from detailed studies of sugar cataracts, either produced experimentally or in animal models with congenital diabetes. One of the most important areas of ongoing NEI research is the assessment of the role of the enzyme aldose reductase (AR) in triggering sugar cataract formation and the evaluation of the efficiency of AR inhibitors in delaying sugar cataracts. The studies of the role of AR in human diabetes have begun only recently. Other ongoing studies include investigations of the role of nutrition in cataract formation and the metabolism of proteins, especially crystallins, during the formation of diabetic and metabolic cataracts.

The NEI is currently supporting research on genetic cataracts involving four different mouse models. Dog and rat models are also being developed. However, very little research involving human genetic cataract, other than descriptive studies of human cataracts associated with chromosome abnormalities and the attempt to culture lens cells for long periods of time, is currently being carried out.

NEI-funded studies on cataract induced by environmental and toxic effects include investigations of the cataractogenic effects of radiation: ionizing, microwave, and ultraviolet; the mode of action of potentially cataractogenic drugs; and methods of studying radiation and toxic effects on the lens.

New techniques for the treatment of cataracts such as phacoemulsification, irrigation-aspiration, and other microsurgical instrumentation have resulted in technical improvements in cataract extractions. There are currently two NEI-sponsored clinical trials of the safety and efficacy of cataract extraction and intraocular lens implantation with emphasis on safety, efficacy, and complication rates. Other studies include the comparision of results of various methods of cataract surgery and various methods of aphakia correction following surgery.

Evidence of Program Performance

Kind of Information Available and Being Used To Monitor Program Performance

- Computerized data on the cost and content of funded grants.
- Grants progress reports.
- Published papers, workshops, and symposia.
- Computerized data showing relevance of funded grants to research priorities identified in NEI five-year national plan.
- Smithsonian Science Information Exchange abstracts of vision research projects sponsored by NEI and other organizations.
- Summary statements and priority scores from initial review group review of new or renewal applications.
- Data on Council actions on cataract grant applications (designations of grant applications as High Program Relevance).
- The expertise of the NEI Cataract Program Director and other in-house cataract experts, as well as consultants from the extramural research community.

Evidence Relating Directly to the Stated Objectives of the Program*

Over the past few years, significant progress has been made in understanding the development, maintenance, structure, and function of the normal lens. NEI-supported investigators have also been able to clarify the formation of cataracts produced by diabetes, galactosemia (a genetic error of metabolism), and rubella virus. For the latter two types, means of prevention are available. Moreover, certain cataracts of previously unknown origin are now known to result from chromosomal abnormalities that may either be inherited or occur during gestation.

It is largely because of basic research on aldose reductase inhibitors (drugs that can prevent sugar cataract formation in animals), photooxidation (the toxic effect of ultraviolet light on the lens), ionizing radiation (X-ray cataract), and other lens toxins that we are now on the threshold of being able to treat some of the more common forms of cataract nonsurgically or to prevent them altogether. The discovery and development of several potent inhibitors of aldose reductase have resulted in delaying or preventing diabetic and galactose cataracts in animals and have set the stage for possible clinical trials in diabetic patients.

Studies during the past five years have provided evidence that X-ray-induced cataract is a useful model for investigating the mechanism of human senile cataract. X-ray has also been used to study the ability of the lens to repair damage to its DNA. Many recent studies show that ultraviolet light can be damaging to the lens.

Cataract which develops as a complication of other ocular diseases, such as uveitis, corneal inflammation, and retinitis pigmentosa, can augment an individual's existing visual problems. NEI-supported investigators have clarified the mechanism for formation of cataracts in uveitis, corneal inflammation, and retinal degeneration and are now studying possible means of preventing them. Collaboration has increased and is expected to develop further among cataract investigators and those working on other related eye disorders.

Epidemiologic studies have confirmed the association of cataracts with several factors that may play a role in their etiology. The prevalence of cataracts has been found to be higher in diabetics under 65 years than in nondiabetics. Other studies have found evidence of a positive association between the prevalence of cataracts and the amount of sunlight in a given geographic area. Advances have also been made in developing a standardized system of classifying human cataracts according to type as a basis for comparative research.

That cataracts can result from severe oxidative damage to the lens with the resultant formation of high-molecular-weight proteins has been clearly demonstrated. Characterization of the high-molecular-weight aggregates, which are believed to cause the light-scattering that impairs vision in cataract, is being actively pursued.

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*This represents a consensus of peer panels of experts and the NEI staff.

Although no medical treatment of cataract has been proved effective, recent advances in the surgical treatment of cataract and correction of aphakia have been remarkable. Surgical techniques have been greatly improved to make cataract surgery safer. Microsurgical instrumentation and operating microscopes are now routinely used during cataract surgery. The evolution of better hard and soft daily-wear and extended-wear contact lenses and a wide variety of intraocular lens implants has provided a range of alternatives for the correction of aphakia following cataract extraction.

In addition to these and other advances in our understanding of the mechanisms of cataractogenesis, in technology to document and classify cataractous changes in vivo as well as in vitro, and in collaborative relationships to utilize more efficiently cataract research personnel and material resources, there has evolved an awareness that epidemiologists, biostatisticians, clinical ophthalmologists, and many other specialists are needed if advances in the laboratory are to lead to clinical applications that will benefit patients with cataract.

Other Evidence Suggestive of Program Efficiency, Effectiveness, and Responsiveness

For quantitative evidence of how well the program is achieving the funding priorities set forth in Vision Research--A National Plan: 1978-82, see the tracking table using the previous subprogram structure in the three-page Attachment to this section. (The new subprogram structure that has superseded the one used in the Attachment is shown on page 2.) The Council's 1977 three-volume plan, prepared with the assistance of 150 scientific advisors, was broadly distributed within the ophthalmic, vision research, and eye care communities. For Cataract and for each of the other four NEI programs, the report defined the disease problems or basic research areas covered, outlined goals and objectives, provided an overview of current research support by NEI and other organizations, assessed recent accomplishments, evaluated major research needs and opportunities, recommended program priorities, and forecasted budget and manpower requirements.

In order to assess how effectively the recommendations in the plan have been implemented, the staff developed a tracking system for matching incoming grant applications with the Plan's recommended levels of support for each research priority. The NEI extramural program directors coded grants funded in FY 1978, 1979, and 1980 according to their correspondence to one or more of the Council's recommendations as they appear in the Plan. The program directors have indicated whether the NEI-funded projects have specific or general applicability to the panel recommendations published in the 1977 planning report. The "Other" categories were used in the tracking tables to indicate those ongoing NEI grants that do not have either specific or general applicability to the recommendations. (For convenience, however, grants in "Other" categories were coded as "general.") From these tables one can see at a glance how well the priority areas of research outlined by the Council are covered by the NEI's current portfolio of research grants.

Studies Now Under Way That Will Assess Program Performance

The National Eye Institute's third comprehensive national vision research evaluation and plan for the years 1983-87 is now under way. It is scheduled for publication in winter 1981.

Proposed Studies That Will Assess Program Performance

An Evaluability Assessment of the Cooperative Cataract Research Group (NEI 82-302) is included in the FY 1981 Evaluation Plan. This proposed project will assess the evaluability of the national Cooperative Cataract Research Group (CCRG), a component of the cataract program, which has been viewed as a possible model for organizing and marketing existing research manpower and facilities to attack specific clinical research problems.

Major Problems Cited by Organizations Within the Administration, Congressional Committees and Organizations, and Interest Groups

A major need cited by the House of Representatives Committee on Appropriations in its report on FY 1981 NEI appropriations is for scientific efforts "to understand how human senile cataract develops and how it might be retarded or prevented." In responding to this need, the Cooperative Cataract Research Group was formed in 1980. This is a team of scientists throughout the United States who have pooled their talents and the strengths of their individual laboratories to capitalize on research opportunities in the lens field. The CCRG, which is funded through an NEI consortium grant, emphasizes research aimed at ensuring that the results of basic research are rapidly applied to solving the problem of human senile cataract, the most common form of the disease and a leading cause of blindness throughout the world. The consortium may also prove to be an ideal mechanism for recruiting and training new scientists in lens research. The goals of the Group are to increase the availability of cataractous and normal human lenses for research, to establish a cataract classification center, to organize a data bank for management and analysis of data derived from the study of human lenses, and to foster collaborative research among American scientists interested in the lens. Specific accomplishments of the CCRG have been:

- Organization of a program that emphasizes collaborative research on human lenses and human cataract.
- Establishment of an experimental protocol for analyzing extracted human lenses. During the past year more than 3,000 lenses that in the past would have been discarded after a cursory pathological examination were studied.
- Development and implementation of a system of photographing and classifying cataractous lenses. Approximately 3,000 lenses have been classified according to cataractous changes in different populations.

- Establishment of biochemical and biophysical profiles of certain types of cataractous change in an attempt to identify causative or risk factors.
- Development of systems of in vivo cataract classification which might be used to quantitate cataractous change occurring either spontaneously or under the influence of an anticataract drug.
- Characterization of sulfur oxidation in human nuclear and cortical cataracts.

Other Major Barriers and Issues Relating to Program Performance

- Need to attract investigators from other fields to problems relating to cataract.
- Dearth of controlled clinical trials of new methods and devices for cataract treatment.
- Need for more basic research on the development, structure, and function of the lens and the development of various forms of cataract.
- Need for more epidemiologic investigations into the nature and causes of cataracts, especially senile cataract.
- Lack of adequate data on incidence, prevalence, and cost of cataract.

To overcome these barriers, the following actions have been taken:

- Development, publication, and widespread distribution to the vision research community of a five-year national vision research plan outlining NEI's program priorities.
- Symposia and workshops on specific program topics.
- Funding of the Cooperative Cataract Research Group.
- Program announcements to the NIH Guide for Grants and Contracts.
- Work of NEI Cataract extramural program director in encouraging the submission of specific types of research grant applications.
- Plans for a pilot National Visual Acuity Impairment Survey, envisioned as an ongoing population study to determine trends in the occurrence of eye problems including cataract and to provide clues to their cause.

Documentation

Vision Research--A National Plan: 1978-82. U.S. DHEW Publication No. (NIH) 78-1258, 1978.

1980 NIH Almanac. U.S. DHEW Publication No. (NIH) 80-5, 1980.

CATARACT PROGRAM PLANNING TRACKING

PANEL RECOMMENDATIONS FROM 1977 PLANNING REPORT	FY 77	ADD'L PROJ RECOM FOR FY 1978	FY 78	FY 79	APR 80
	NUMBER OF GRANTS (SPECIFIC/GENERAL)				
30CC CATARACT					
A OTHER (PROGRAM)					
31CC THE NORMAL LENS					
A TRANSPORT, METABOLISM, CHEMICAL COMPOSITION					
A1 BIOCHEMICAL STUDIES	20/4	1	24/4	22/4	25/4
A2 DETERMINE CHEMICAL COMPOSITION OF THE NORMAL HUMAN LENS		1	1/0	1/0	1/0
A3 OTHER (AREA)		0			
B LENS CULTURE					
B1 DEVELOP METHODS FOR CULTURING THE HUMAN LENS AND LENS CELLS		1			
B2 OTHER (AREA)	0/1	0	0/3	0/3	0/3
C LENS EMBRYOLOGY					
C1 DEVELOP/APPLY TECHNIQUES FOR STUDYING LENS FIBER/ZONULE EMBRY./MORPHO.	1/1	1	1/1	1/2	1/2
C2 OTHER (AREA)	0/1	0	0/2	1/2	0/2
D PROTEIN CHEMISTRY					
D1 (SEE RECOMMENDATION A1 ABOVE)		1			
D2 APPLY NEW TECH. FOR STUDYING LENS TRANSPARENCY & LIGHT TRANSMISSION		1			
D3 OTHER (AREA)	0/1	0	0/1	0/1	0/1
E MOLECULAR BIOLOGY					
E1 (SEE RECOMMENDATION A1 ABOVE)		1			
E2 OTHER (AREA)	0/2	0	0/4	0/4	0/4
F OTHER (SUBPROGRAM)	0/3	0	0/1	0/3	0/3
SUBPROGRAM TOTAL:	21/13	7	26/16	25/19	27/19
32CC SENILE OR DEGENERATIVE CATARACT					
A CAUSES AND PATHOGENESIS					
A1 ESTABLISH A COOPERATIVE CATARACT RESEARCH GROUP		**		1/0	1/0
A2 DEVEL./APPLY NEW BIOCHEM./BIOPHYS. TECH. TO STUDY SENILE LENS/CATARACT	0/1	--	0/1	0/2	0/1
A2A PROTEINS	1/4	2	5/3	4/3	5/3
A2B ELECTROLYTES		2			
A2C LIPIDS	0/1	3	1/1	1/1	1/2
A2D CARBOHYDRATES		3			
A2E PEPTIDES		2			
A2F OTHER (SUBAREA)	0/4	0	0/4	0/4	1/4
A3 DEVELOP METHODS FOR CULTURING SENILE CATARACT		1			
A4 DESIGN EQUIP. TO DOC. CHANGES SENILE HUMAN LENS AND CATARACT DEVEL.	0/2	*	0/3	0/2	0/2
A5 OTHER (AREA)	0/1	0	0/2		0/3
B TREATMENT					
B1 ORGANIZE LARGE-SCALE CLINICAL TRIALS OF INTRAOCULAR LENSES	1/0	*		1/0	2/0
B2 STUDY INTRAOCULAR LENSES IN ANIMALS		1	1/0	1/0	1/1
B3 OTHER (AREA)		0			
C EPIDEMIOLOGY					
C1 EXPAND EPIDEM. INVEST. INTO NATURE/CAUSES OF SENILE CATARACTS		1			
C2 OTHER (AREA)		0			
D OTHER (SUBPROGRAM)	0/1	0			
SUBPROGRAM TOTAL:	2/14	15	7/14	8/14	11/16

KEY

//	COUNTED IN ANOTHER SUBPROGRAM		
--	COUNTED BELOW IN SUBAREA(S)		
*	CENTER OR CONTRACT SPECIFIED	()	COUNTED IN PRECEDING NUMBER
**	SPECIAL MECHANISM SPECIFIED	BLANK	SUBPROGRAM TITLE

CATARACT PROGRAM PLANNING TRACKING

			NUMBER OF GRANTS (SPECIFIC/GENERAL)		
PANEL RECOMMENDATIONS FROM 1977 PLANNING REPORT	FY 77	ADD'L PROJ RECOM FOR FY 1978	FY 78	FY 79	APR 80
3300 DIABETIC CATARACT					
A CAUSATIVE MECHANISMS				0/3	0/3
A1 STUDY THE CHEMICAL PATHWAYS INVOLVED IN DIABETIC CATARACT		2	0/2	0/2	0/2
A2 OTHER (AREA)		0			
B PHARMACOLOGIC CONTROL					
B1 DELAY DIABETIC CATARACT FORMATION WITH DRUGS OR CHEMICALS		2	1/1	1/1	2/1
B2 OTHER (AREA)		0			
C OTHER (SUBPROGRAM)	0/1	0	0/1	0/2	0/2
SUBPROGRAM TOTAL:	C/1	4	1/4	1/8	2/8
3400 CONGENITAL, METABOLIC, AND GENETIC CATARACTS					
A GENE REGULATED DIFFERENTIATION OF LENS FIBERS					
A1 STUDY CHROMOSOMAL CHARACTERISTICS IN HUMANS/LAB. ANIMALS WITH CATARACT	1/1	*	1/3	2/3	2/2
A2 OTHER (AREA)	0/1	C			
B SYSTEMIC METABOLIC ABNORMALITIES					
B1 DETERMINE INBORN ERRORS OF METABOLISM THAT CAUSE CATARACT		*			
B2 OTHER (AREA)		0		0/1	
C VIRUS-INDUCED CATARACTS					
C1 INVESTIGATE THE CATARACTOGENIC EFFECTS OF VIRUSES		1			
C2 OTHER (AREA)		C			
D CALCIUM EFFECTS					
D1 INVEST. EFFECTS OF CA IONS ON NORMAL LENS/IN HYPOPARATHYROIDISM		1			
D2 OTHER (AREA)		C			
E TISSUE CULTURE					
E1 STUDY LENS EPITHELIAL CELLS AND FIBERS IN TISSUE CULTURE		2	0/1	C/1	0/1
E2 OTHER (AREA)		0			
F OTHER (SUBPROGRAM)		0	0/2	0/2	0/2
SUBPROGRAM TOTAL:	1/2	4	1/6	2/7	2/5
3500 CATARACT INDUCED BY DRUGS & RADIATION/SECONDARY CATARACT					
A DRUG-INDUCED CATARACTS					
A1 DET. DOSE/RESPONSE CHARACTER. OF DRUGS WHICH INDUCE HUMAN CATARACTS		1			
A2 TEST DRUGS IN LAB. ANIMALS/LENS CULTURE PRIOR TO ADMIN. IN HUMANS		1			
A3 OTHER (AREA)	C/5	C	0/6	C/4	0/4
B ULTRAVIOLET LIGHT IN CATARACTOGENESIS					
B1 CONDUCT CONTROLLED STUDIES OF OCULAR EFFECTS OF UV LIGHT	1/C	1	1/0	1/0	1/8
B2 OTHER (AREA)	C/1	C	0/5	0/4	0/4
C CATARACTS IN OTHER EYE DISORDERS					
C1 DET. ROLE OF PHOSPHOLIPIDS IN CATARACTS SEC. TO UVEITIS, INFLAM., RP		2			
C2 OTHER (AREA)		0			
D OTHER (SUBPROGRAM)	C/3	0	0/3	0/1	0/1
SUBPROGRAM TOTAL:	1/9	5	1/14	1/9	1/9

KEY

//	COUNTED IN ANOTHER SUBPROGRAM
--	COUNTED BELOW IN SUBAREA(S)
*	CENTER OR CONTRACT SPECIFIED
**	SPECIAL MECHANISM SPECIFIED
( )	COUNTED IN PRECEDING NUMBER
BLANK	SUBPROGRAM TITLE

CATARACT PROGRAM PLANNING TRACKING

PANEL RECOMMENDATIONS FROM 1977 PLANNING REPORT	FY 77	ADD'L PROJ RECOM FOR FY 1978	NUMBER OF GRANTS (SPECIFIC/GENERAL) FY 78	FY 79	APR 80
3600 DISLOCATED LENS					
A ZONULAR STRUCTURE AND FUNCTION					
A1 INVESTIGATE THE MORPHO. STRUCTURE/CHEMICAL COMP. OF ZONULES		1			
A2 OTHER (AREA)		0			
B GENETICS					
B1 IDENTIFY METAB. ABNORMAL. IN GENETIC DISORDERS ASSOC. W. DISLO. LENSES		N			
B2 OTHER (AREA)		0			
C THERAPY					
C1 DISLO. LENS EFFECT ON V.A., PREV. AMBLYOPIA IN CHILDREN BY EARLY SURG.		N			
C2 OTHER (AREA)		0			
D OTHER (SUBPROGRAM)		0			
SUBPROGRAM TOTAL:	0/0	1	0/0	0/0	0/0
3700 ACCOMODATION AND OPTICAL PROBLEMS OF CATARACT AND APHAKIA					
A ACCOMODATION					
A1 INVEST. RELATIONSHIPS BET. CIL. BODY & LENS; EFFECTS UPON THE RETINA		1			
A2 OTHER (AREA)		0	0/1	0/1	0/1
B OPTICAL PROBLEMS AFTER CATARACT SURGERY					
B1 STUDY THE RESTORATION OF MORE NORMAL VISION IN APHAKIA		N			
B2 STUDY OPTIMIZ. VIS. FUNC. IN CHILDREN WITH CATARACT BEFORE/AFTER SURG.		N			
B3 OTHER (AREA)		0			
C OTHER (SUBPROGRAM)		0			
SUBPROGRAM TOTAL:	0/0	1	0/1	0/1	0/1
PROGRAM TOTAL:	25/39	37	36/55	37/58	43/58

KEY

//	COUNTED IN ANOTHER SUBPROGRAM
--	COUNTED BELOW IN SUBAREA(S)
N	CENTER OR CONTRACT SPECIFIED
NN	SPECIAL MECHANISM SPECIFIED
()	COUNTED IN PRECEDING NUMBER
BLANK	SUBPROGRAM TITLE

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Director's Overview

The budget of the National Institute of General Medical Sciences (NIGMS) is dedicated to the support of basic research performed by investigators at universities, medical schools, and similar institutions throughout the country. These activities undergird the research areas of all the other categorical institutes.

Since this research is undifferentiated, priority for support is based primarily on an assessment of opportunities for major advances in knowledge and on the probability that new findings will ultimately contribute to improved prevention, diagnosis, or treatment of disease.

It is characteristic of the basic research projects supported by the Institute that they evolve and change character, often in an applied direction, when circumstances and opportunities warrant. As this happens, the investigator's activities may become more appropriately supported by one of the categorical institutes, and the grant is transferred accordingly. In other words, there is a continuing turnover of grants supported by NIGMS such that new ideas and new investigators can be tested constantly and given a chance to contribute to biomedical knowledge. In the aggregate, the Institute's grantees constitute an essential national resource that continually generates new ideas and knowledge. But this resource must be maintained and carefully nurtured, and, while the Institute is always alert to new opportunities and initiatives, it also recognizes a responsibility to minimize the impact of budgetary instability and rapid policy changes. Changes of commitment and direction on short notice lower the productivity of university research laboratories.

Consistent with its mission to support basic, undifferentiated research, the Institute's programs of applied and clinical research are relatively small. In trauma and burn research and anesthesiology, the Institute will continue to give special emphasis to relevant physiologic and biochemical investigations. A knowledge of the key physiologic functions in these patients cannot prevent trauma, but should allow more effective intervention and prevention of post-traumatic complications. A better understanding of the clinical pharmacology of anesthetic agents is essential in order to increase the safety and efficacy of anesthesia.

It is our conviction that the ultimate result of the basic, laboratory-oriented research supported by NIGMS will be the prevention of much illness whose nature we do not now understand. At this stage, however, we have no way of knowing which illnesses will be preventable, since prevention will depend almost entirely on laboratory advances that cannot now be foreseen. In setting priorities, we are conscious of the observation that such advances are often not correlated with the size of assigned program budgets, but that they always require the presence of scientific opportunities. As to the choice among those opportunities, it should be remembered that it is in the grant applicant's professional self-interest to seek out the most promising of these opportunities. We also have evidence that, beyond this motive, our grantees also have strong humanitarian incentives to have their work not only widely communicated, but applied toward improved health care.

Further, it is our conviction that exciting research opportunities will continue for many years in the fields of genetics, molecular and cellular biology, and pharmacology. In order to fully mine these areas, well-trained, highly qualified research scientists must be available. Thus, the NIGMS program of support will continue for first-rate predoctoral research training which provides multidisciplinary background knowledge and "hands-on" experience in the broad fields mentioned above. Such training is best done through integrated, carefully planned programs at those institutions which have proven track records as shown by the accomplishments of their graduates. It should be emphasized that today's trainees will not have a significant impact in the research arena for about 10 years. This, again, indicates the importance of such research training activities for prevention of disease and also emphasizes that it is not a large number of students that is required, but their quality and the quality of their opportunities for training.

FY 1981, Areas of Promise

Genetics

- Progress in genetics has burgeoned in the past several years and there is every indication that an explosion of knowledge will continue. It has become clear that genes are not static pieces of DNA arranged in a chromosome but can move around, be transposed, or be present in repeated segments in the chromosome. The phenomenon referred to as "jumping genes," the ability of portions of chromosomes to move around, has now been recognized to be responsible for the tremendous diversity of proteins and antibodies that an individual can produce. Basic studies in this area may prove important to our understanding of the origin of genetic aberrations associated with cancer and other diseases.

- Analysis of eukaryotic chromosome structure is offering clues to how the genetic information encoded in the nucleus of each cell in the body is expressed, and especially how that expression may be regulated. The fact that cells differ in major characteristics, while possessing the same genetic information, poses a major problem in biology whose solution will probably have relevance not only to our understanding of human development, but also of (1) aging, (2) neoplasia, (3) activation of latent virus, (4) triggering of "genetic" disease, and (5) the effects of drugs. There are hints that the kind of recognition or molecular matching exemplified by the antigen-antibody reaction will turn out to be a model for understanding other subcellular processes, including genetic expression.

Membrane Research

- Understanding the structure and function of cell membranes has resulted in the following: (1) the discovery of specific "receptors" on neurons for a growing number of transmitters, including oligopeptides; (2) the discovery that cells have specialized receptors which recognize specific circulating enzymes and participate in their uptake. This has important implications for replacement therapy of various genetic diseases caused by the lack of particular enzymes; (3) indications that the number of insulin receptors is related to the concentration of insulin in the plasma. This has great significance for our understanding of the control of insulin and blood glucose levels in the body, and, by analogy, of other regulatory endocrine mechanisms; (4) indications that other blood constituents, such as lipoproteins, also seem to have specific "target" cells.

  Further research advances in this area could hold the key to major breakthroughs in the prevention, diagnosis, and treatment of various genetic, endocrine, cardiovascular, neoplastic, immunologic, and neurologic diseases. Because of a number of recent technical advances in identification and isolation of membrane components, increased opportunities for progress are now at hand.

Metal Ions and Regulation

- Calcium is emerging as a particularly important element central to intracellular regulation of energy metabolism and cellular contractility. The major determining factor in the action of calcium seems to be the local concentration of the free ionized form, which results from interconversion with protein-bound calcium or other forms of "storage," on the one hand, and transport across the plasma or intracellular membrane on the other. Calcium ions also are assuming increasing importance as control points for such diverse cell processes as response to hormones, cell movement, and fertilization.

- Iron sulfur (Fe-S) proteins are in a new class of proteins. Discovered through the use of sophisticated new techniques, these proteins have now been found in a wide range of organisms, and are believed to be vital to many biological processes. This opens up a whole new area of research directed toward understanding the origin of disease.

- A highly promising area of research is the characterization of receptors for drugs and neurotransmitters in the intact organism. Many diseases and some types of drug resistance are now thought to be due either to defective receptors with decreased affinity for their natural substrates or to decreased numbers of receptors. In addition, many drugs have now been shown to be effective because of their affinities for specific receptors; and knowledge of the properties of these receptors may make possible design of more specific and effective drugs. So-called computer graphics is a new tool that promises to speed the development of new, more effective drug molecules. While isolation and identification of these receptors has progressed rapidly employing biochemical techniques, only very recently have productive methods begun to be applied to the whole animal or to human investigation.

Burn Research

- Two longtime NIGMS grantees, Dr. I. V. Yannas of Massachusetts Institute of Technology and Dr. John Burke of the Massachusetts General Hospital, have recently won wide acclaim for their successful development of an artificial skin to help treat individuals who have suffered from severe burns. Seven patients, 5 to 60 years of age, having third-degree burns over 60 to 90 percent of their bodies, received grafts of this artificial skin over the past 15 months. To date, the material has not been rejected by any of the patients, nor have any infections--the chief cause of death from burns--developed in any of the grafted areas.

FY 1982 Program Changes

Fiscal constraints in 1982 will necessarily dampen the exciting progress that might have been anticipated. The Institute's various programs will feel the impact of inflation, and we expect that only about two out of five investigators having approved applications will be funded. This will lead to a worrisome distortion of several aspects of our support of biomedical research. Many applicants do not consider these to be favorable odds, and increasing numbers of potential investigators will never enter productive research careers, but, rather, will turn to other pursuits and professions. The resultant loss of new scientists with novel approaches will rob our national scientific resource of some of its vitality. Another effect may be seen in the character of the research proposals. While all research is risky in the sense that the outcome is essentially unpredictable, proposals that build on unorthodox assumptions are especially risky. When only a small proportion of approved projects are funded, applicants are understandably reluctant to take great risks. Nevertheless, the Institute will continue to look for daring proposals and to identify and fund the best among them.

- Given the particular mission to support undifferentiated, basic research, the Institute would give some preference to funding of research applications in the CMBD (Cellular and Molecular Basis of Disease) and Genetics Programs at the expense of more applied and clinical research.

- Within the more applied and clinical programs, research center grants will be deemphasized.

- The support of research training is at a level that would fund the same number of individuals as in 1980 and 1981, giving continued emphasis to predoctoral training. The rationale for this, in face of the decreased research grant budget, is that research training is addressing needs that are five to ten years in the future, and that the feedback loop, therefore, is too long to correct any errors quickly. We think the best way to minimize errors of that kind is to conservatively maintain the current numbers of stipends. In this we are also following the latest recommendations of the National Academy of Sciences.

In summary, the following are the major features of this budget:

- Inability to respond to new scientific opportunities.

- Deemphasis of applied and clinical research programs.

- Maintenance of number of individuals supported by National Research Service Awards (NRSA).

FY 1983 Program Changes

At the budget level planned in FY 1983, the effects of inflation on the support of biomedical research probably will be neutralized.

- Little if any expansion of ongoing activities will occur, but attempts will be made to maintain the momentum in the promising areas mentioned above by funding as many meritorious investigator-initiated research grants as possible.

- Trauma and Burn Research. Over the last few years, Institute grantees have made substantial progress in establishing the fluid and nutritional requirements of trauma and burn patients, and many of the advances have been published in a widely distributed manual. Further improvements are needed, however, and this necessitates basic studies, at the cellular and molecular level, of the profound biochemical systemic changes that follow severe trauma and burns. In order to further encourage research on these problems, the Institute is continuing to let the scientific community know of its strong interest in trauma and burn research, and the availability of support for new investigators and for research training of future investigators in this area.

- Research Training

  --Emphasis, within the limited funds, will be placed on predoctoral, multidisciplinary training, including the programs which constitute an important subset of the predoctoral multidisciplinary research training programs, in that they encourage trainee applicants to seek combined medical and scientific training, leading to the M.D.-Ph.D. degree.

--The Minority Access to Research Careers (MARC) Program will be reassessed, since the lack of "trainee-related expenses" (institutional allowances) will have a severe impact which threatens the viability of the Honors Undergraduate Program. Discussions are underway related to the use of whatever funds are available under the MARC and Minority Biomedical Support (MBS) Programs in the most effective manner.

Efforts will be made to start the predoctoral individual fellowship program.

--The postdoctoral (post-Ph.D.) training grants will be deemphasized and support for such individuals will be provided, on a limited scale, by the award of individual fellowships.

- Research Resources. As part of a recognition of the need for research resources, the Institute plans to support the development of a nucleic acid sequence data bank to store and make available the results of research in the burgeoning area of polynucleotide structure and function. The rapid pace of developments in this field has caused concern that the traditional scientific journals may not be able to continue to publish these data and, consequently, a need has been perceived for the development of a computerized system for storing and retrieving this information. The proposed system would permit verification of experimental results before they are entered into the data bank, storage of all pertinent information on the structure and biological expression of each new polynucleotide, and interrogation of the data base by research investigators.

Potential Impact of Program Changes on Three-Year Period (1983-1985)

Given annual budget increases that offset inflation, the Institute will be able to maintain its support of fundamental research in molecular and cell biology, genetics, and pharmacology, and to continue the investigations on the systemic effects of major trauma, including burns. The control of genetic expression and membrane structure and function stand out as particularly promising areas of support.

The Institute is concerned about the lack of stable support for predoctoral research training and a possible drop in the influx of young, creative minds to biomedical science, threatening our Nation's future capability in this regard. Continued emphasis will therefore be placed on stabilizing this extramural activity, which includes the Medical Scientist Training Program. Stability in this context must not lead to stagnation, and competition through peer review is critically important.

NIGMS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

DATE: JAN 3 0 1981

TO : Director
National Institute of General Medical Sciences

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I would like to take this opportunity to acknowledge again the stabilizing influence which your Institute exerts in the support of science underlying progress in the categorical disease areas. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

DS Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

The NIGMS plan stresses the need for (1) continued efforts to stabilize the research science base through sustained emphasis on support of investigator-initiated research grant projects, (2) production of future investigators through a continuing commitment to the support of predoctoral trainees, and (3) strengthening the research environment by encouraging the replenishment of obsolete research equipment, promoting the sharing of expensive research instruments, facilitating the exchange of information, and increasing access to unique research materials.

Impact of Stabilization

- The number of competing research project grants (R01s) to be supported in 1981 represents a slight decrease from the number supported in 1980. In 1982 this number will increase modestly but will remain below the 1980 level.
- Support for program projects in 1981 and 1982 will remain at the 1980 level.
- The number of research centers will be held almost constant in 1981 and 1982.
- An increase in funds will be provided for training in 1981, and another modest increase is planned for 1982.
- No major program changes are planned for FY 1982 although special attention will be directed toward protecting the base of research within two program areas of special importance to the mission of NIGMS--the CMBD and Genetics.

Training

- In FY 1982, the NIGMS will continue its strong commitment to the support of predoctoral research training.
- The Medical Scientist Training Program (MSTP), which leads to a combined M.D.-Ph.D. degree, will be funded at a level of approximately $9.0 million and will graduate about 120 students per year. Preliminary observations indicate that 70 percent of the graduates of the MSTP program are performing research in academic medical settings. A follow-up study is being conducted to determine the effectiveness of the program in directing individuals to careers in clinical research.

- The NIGMS has proposed a MARC individual predoctoral fellowship to encourage graduates of the MARC Honors Undergraduate Research Training Program to matriculate in the best biomedical predoctoral training programs available. The Institute had proposed that, in addition to funds for a predoctoral stipend and for tuition, an allowance of $3,500 be provided for fees, supplies, and travel in order to provide funds which are comparable to those available for trainees supported under NRSA predoctoral institutional fellowship awards. Participation in this program would be limited to the very best graduates of the MARC Undergraduate Research Training Program.

Research Resources

- The Institute plans to support the development of a nucleic acid sequence data bank to store and make available the results of research in the burgeoning area of polynucleotide structure and function. The rapid pace of developments in this field has caused concern that the traditional scientific journals may not be able to continue to publish these data and, consequently, a need has been perceived for the development of a computerized system for storing and retrieving this information. The proposed system would permit verification of experimental results before they are entered into the data bank, storage of all pertinent information on the structure and biological expression of each new polynucleotide, and interrogation of the data base by research investigators.

Fiscal Year 1983

- If no additional funds were provided for 1983, the balance between investigator-initiated research grant projects and research centers would be maintained, and research training would be set at a dollar level that would permit funding approximately the same number of individuals as trained in FY 1982.

- If a modest increase in funds were provided, it would permit (1) the restoration of the previous balance between basic and applied research; (2) an increased emphasis on research on control of gene expression, both in regard to temporal and functional differentiation; (3) a response to the major new opportunities in studying membrane proteins that have resulted from new genetic and analytical techniques; (4) strong encouragement of investigations of cellular drug receptors in order to increasingly tailor-make drugs to act on specific, desired target cells or organs, thus minimizing adverse effects of therapy; and (5) restoration of research training to the 1979 level with regard to the number of individuals supported.

- If a significant increase in funds were provided, over half the approved research grant applications would be funded, research training support would be increased, and the following initiatives would be undertaken: (1) major encouragement of research on genetic recombination and studies on transposable genetic elements; and (2) stimulation of research on the full gamut of proteins associated with all aspects of transcription and translation of DNA.

Action Items

The NIGMS will develop estimates of the total costs that might be incurred in the operation of a system for the storage and retrieval of information on the structure and function of polynucleotides. The Institute will determine the possibilities that may exist for co-funding this activity with other NIH Institutes and with other agencies both in this country and abroad. (This information was provided by the NIGMS in a meeting with Dr. Fredrickson on January 5, 1981.)

The status of the proposal by the NIGMS to initiate a MARC individual predoctoral fellowship should be checked. In the interim, the NIGMS will continue to develop a modified version of the original proposal, which is patterned after an existing ADAMHA* fellowship. (An announcement of a MARC Individual Predoctoral Fellowship, following the ADAMHA model, was published in the NIH Guide for Grants and Contracts, Vol. 10, No. 1, January 2, 1981.)

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* Alcohol, Drug Abuse, and Mental Health Administration

MARC Individual Predoctoral Fellowship

Statement of Issue

Support guidelines for MARC individual predoctoral fellowship.

Discussion of Issue

We propose that, in addition to funds for a predoctoral stipend and for tuition, an allowance of $3,500 be provided for fees, supplies, and travel. This sum has been chosen in order to provide funds which are comparable to those available for trainees supported under NRSA predoctoral institutional fellowship awards. The latter provide $3,000 in non-trainee expenses in addition to separate funds for trainee travel. Since the purpose of the MARC predoctoral fellowship is to strongly encourage graduates of the MARC Honors Undergraduate Research Training Program to matriculate in the best biomedical predoctoral training programs, most of which have predoctoral support under NRSA institutional fellowship awards, the need for comparability is essential.

We are aware that the ADAMHA individual predoctoral fellowship program provides an allowance of $4,000 to cover expenses such as tuition and fees, supplies, etc., and that this is quite different from what NIGMS is proposing. Based on our analysis of tuition costs, the $4,000 allowance provided by ADAMHA cannot be considered anything but partial payment.

PROGRAM PERFORMANCE SUMMARY

MINORITY ACCESS TO RESEARCH CAREERS

Program Description

Problems Addressed

The Minority Access to Research Careers (MARC) Program is a research training program for faculty members and students at minority institutions having health-related research activities. It is composed of a predoctoral and postdoctoral faculty fellowship program, a visiting scientist program, an honors undergraduate research training program, and an individual predoctoral fellowship program.

The impetus to develop and launch the MARC Program in 1972 came about from full recognition of: (1) the low proportion of minority group members among the Nation's biomedical scientists, (2) the apparent lack of improvement of this situation following a decade or more of rather generous funding of NIH research training programs, (3) the resulting, potential loss of scientific talent from an important segment of our society, and (4) the ever-increasing demand for recruitment of minority group scientists by academic institutions, industry, and government.

The proportion of U.S. citizens holding doctoral degrees who are members of minority groups is strikingly lower than the percentage of minority group U.S. citizens. Also, according to a 1979 survey of doctorate recipients by the National Academy of Sciences, members of racial/ethnic minority groups numbered 28,400 and accounted for 9 percent of the total population of doctorate recipients in science and engineering. Only 1.1 percent of persons holding a Ph.D. in science and engineering are black. The number of doctorates, both M.D.'s and Ph.D.'s, for other non-Asian minority groups, such as Chicanos and American Indians, is proportionally even lower than for blacks.

The number of blacks and members of other minority groups currently being trained for the doctorate is correspondingly small. Even in recent years, less than 1 percent of the Ph.D. candidates in U.S. graduate schools were black men and women (of U.S. citizenship). Yet it is interesting to note that a 1974 National Science Foundation report states that 16 percent of the full-time graduate students enrolled in the sciences in these institutions were non-U.S. citizens. By contrast, the demand throughout the Nation for Ph.D.'s in the biomedical sciences from among blacks and other minority group U.S. citizens is unprecedented. Vigorous recruitment is under way throughout the Government, academic institutions, hospitals, research institutions, and industry for the few well-trained individuals who are available.

Legislative History

The Secretary of Health, Education, and Welfare is mandated under Section 301 of the Public Health Service Act (42 U.S. Code 241) to support and encourage research, education, and training in the health fields and biomedical communications. Section 301 states in part that the Secretary makes "grants-in-aid to universities, hospitals, laboratories, and other public and private institutions."

In June 1972, the Minority Access to Research Careers (MARC) Program was initiated and developed under the authority of Section 301. Through this program, the National Institute of General Medical Sciences (NIGMS) provided support for research training in the basic biomedical sciences for faculty members at minority institutions.

The reaction of the Congress to this initial effort was most positive, as characterized by the Senate HEW-Labor Appropriations Committee Reports of 1972 and subsequent years in which there appears language specifically directing that the MARC Program of NIGMS make use of funds for the purposes designated therein. Following up on this directive, the Institute again solicited applications, was encouraged by the response, and in June 1974, awarded Faculty Fellowships, Visiting Scientist Awards, and training grants totaling in excess of $4.5 million.

The enactment of the National Research Service Award Act of 1974 (P.L. 93-348) repealed the research training authority of Section 301 of the PHS Act and provided a new research training authority for all of NIH--the National Research Service Award. Although P.L. 93-348 enabled MARC to continue to fund the Faculty Fellowship portion of the MARC Program, it made no provision for Visiting Scientist Awards.

In May 1976, under the authority of the Health Research and Health Services Amendments of 1976 (P.L. 94-278), Title XI, Sec. 1103, the NIGMS announced its Visiting Scientist Award. These Visiting Scientist Awards are made to enable the faculty and students of minority institutions to receive guidance and advice with regard to research, teaching, and curriculum development in the biomedical and behavioral sciences from recognized scientific experts.

In HEW appropriation bills for 1973 and subsequent years, the Congress has made clear its support for an undergraduate portion of the MARC Program. In the 1977 appropriation, the Senate Appropriations Committee provided an increase of $3.7 million in the NIGMS budget for the MARC Program, stating "The Committee directs the Institute to report to the Committee as to their spending plans for these funds." Based on its interpretation of Section 472 (a) (1) (A) (iv) of Title I of the National Research Act (42-USC-4821-1) that the authority for National Research Service Awards for biomedical and behavioral research provides for pre- and postdoctoral training, NIGMS implemented the MARC Undergraduate Research Program in 1977.

The MARC Honors Undergraduate Training Program is aimed primarily at strengthening undergraduate research training programs in the biomedical sciences at minority institutions and should significantly increase the number of well-prepared minority students who will compete for candidacy in graduate schools offering the Ph.D. degree. In addition, it aids such institutions in developing intensive and in-depth biomedical sciences curricula.

In January 1981 the newest component of the MARC Program, the MARC Individual Predoctoral Fellowship, was announced under the authority of Section 472 of the Public Health Service Act as amended (42 USC 2891-1). The first receipt date for applications was February 1, 1981, and the Institute funded a few awards in FY 1981. This fellowship program provides support for research training leading to the Ph.D. degree in the biomedical sciences for selected students who are graduates of the MARC Honors Undergraduate Research Training Program. It is expected that such training will be conducted in graduate schools of the highest quality.

Funding and Staffing, 1978-82

Staff directly related to the program are a Program Director, an Education Specialist, and 2 secretaries. The Institute also has a consultant, Dr. Geraldine Woods, who attends review committee meetings, site visits, minority conferences, and Council meetings. Dr. Woods provides advice to the Director of the Institute regarding the development of policy for the MARC program and its relationship to other minority educational efforts in the public and private sector.

It should be noted that the review of training grants, site visits, program planning and evaluation, and other functions all require considerable program, grants management, and review staff. The MARC Program comprises 1.5 percent of the Institute's total grants budget. Noting that the total Institute program staff is 51 persons, the prorated share of the total MARC program staff, based on funding level, is approximately 0.7 people.

Relationship to the DRR Minority Biomedical Support (MBS) Program

The Division of Research Resources (DRR) started its MBS program in 1971 and made the first awards in June of 1972. The goals of this program are: " . . . to increase the numbers of ethnic minority faculty and student investigators in the biomedical sciences and to broaden the opportunities for research and research participation by ethnic minorities."

The MBS Program, however, is oriented toward the institution rather than the individual researcher, leaving the institution itself to focus on ways of providing greater opportunity for minorities to pursue biomedical research careers. The MARC Program is, on the other hand, oriented directly toward the individual's need and plans for research training, in line with the general NIGMS mandate for research training. Hence, these two programs are independent, yet mutually supportive and complementary.

MARC Program Awards by Amount, Number, and Number of Trainees (FTEs), and by Program Area, 1978-81

(Dollars in Thousands)

Program area	1978			1979			1980			1981		
	Amt.	No. of awards	FTEs	Amt.	No. of awards	FTEs	Amt.	No. of awards	FTEs	Amt.	No. of awards	FTEs
Faculty fellowship												
Predoctoral	$322	18	18	$361	20	20	$344	16	16	$210	8	8
Postdoctoral	398	20	20	303	14	14	153	7	7	263	12	12
Visiting scientist	2	2	2	0	0	0	0	0	0	3	1	1
Honors undergraduate	1,285	17	112	1,804	22	163	3,271	35	237	3,508	39	286
Institutional												
Predoctoral	564	7	77	402	4	43	542	4	43	542	4	43
Individual												
Predoctoral	-	-	-	-	-	-	-	-	-	36	4	4

Program Objective and Activities

Program Objective

The principal objective of the Minority Access to Research Careers Program is to increase the number of minority scientists engaged in biological research by:

- Providing opportunities for selected faculty members of minority institutions to pursue advanced training in biomedically related research in major research universities and laboratories beyond their home institutions.
- Attracting outstanding scientists from other major institutions for periods of in-residence teaching and science counseling to minority institutions.
- Developing and strengthening the overall undergraduate research training programs with an intensive, in-depth, honors biomedical sciences curriculum and other special activities.
- Specifically increasing the number of well-prepared undergraduate minority students who will subsequently compete successfully as candidates for the Ph.D. degree in the Nation's quality graduate schools.

Background and Current Program Activity

The first component of the MARC Program was initiated in 1972 as a modest undertaking to support faculty members of predominantly minority institutions who elected to attend major institutions of higher education to pursue either postdoctoral research training or to complete the requirements for the Ph.D. degree in the biomedical sciences. This is known as the "MARC Faculty Fellowship Program." A second component is the "MARC Visiting Scientist Program." It allows minority institutions to identify prominent scientist-scholars from around the country who wish to come to such institutions for periods of time ranging from one academic quarter to one full year in order to assist in strengthening the institutions' research training endeavors related to the biomedical sciences.

Establishment of both of these components of the MARC Program has been lauded by the Congress, in successive House and Senate Appropriations Subcommittee Reports, and by the biomedical scientific community. The minority institutions have welcomed particularly the MARC Faculty Fellowship Awards. A higher proportion of the science faculty in these institutions, compared to the majority of U.S. academic institutions, do not hold the doctorate. Also, due to unusally heavy teaching loads, many of those who do hold the Ph.D. degree have not been able to stay abreast of current research advances, methods, and techniques. The MARC Faculty Fellowship Program has already had a significant impact in helping to correct this situation.

The MARC Program currently supports MARC Faculty Fellows at graduate research institutions and laboratories throughout the country in the following research areas: cellular and molecular biology, genetics, pharmacology and toxicology, physiological sciences, biomedical engineering, cancer biology, infectious diseases, and heart, lung, and blood research.

To date, the Visiting Scientist Award Program has been underutilized. Only three awards have been provided, based on eight applications considered. Considerable advance planning by the host institution and the prospective visiting scientist is required for this program, and some uncertainty about the status of the MARC Program from time to time has tempered a fuller development of this aspect of the program. Strong continued efforts to advertise and encourage the utilization of the Visiting Scientist Award are being made by NIGMS. The MARC Review Committee has strongly urged continuation of this award mechanism.

The central goal of the MARC Program remains that of increasing the number of highly qualified minority group biomedical scientists. To accomplish this objective, a marked increase in the enrollment of minority group students as Ph.D. candidates in major universities throughout the country must first be achieved. Sound preparation of even the most outstanding students during their undergraduate years must precede their successful entrance into graduate school. Among black students who have earned the Ph.D. degree, the great majority completed their undergraduate work at predominantly black colleges and universities. All recent studies suggest that these same black undergraduate schools are still preparing the majority of students who are successful in entering graduate and professional school programs, even though a much greater number of black students are now enrolled in undergraduate programs of the Nation's major universities. It is for these reasons that the MARC Program, through its MARC Honors Undergraduate Research Training Program, focuses on strengthening the traditional minority institutions toward developing a pool of highly qualified predoctoral candidates. There are currently 39 programs supporting 286 trainees.

As previously stated, the MARC Predoctoral Fellowships will support biomedical research training leading to the Ph.D. degree in the biomedical sciences for selected students who are graduates of the MARC Honors Undergraduate Program. The Institute has made a few awards to individuals of academic excellence in FY 1981.

Evidence of Program Performance

Program Monitoring

The honors undergraduate program is monitored by means of periodic reports from the undergraduates and their preceptors. Of chief interest, since this program is intended to place increased numbers of minority students in graduate schools of the Nation's major institutions, is the number entering such graduate schools and the choice of schools at which they matriculate. These include some of the best graduate programs in the United States; i.e., Harvard, MIT, Yale, U. California, Stanford, Washington

University (St. Louis), Brown, Duke, Baylor, Columbia, Texas A&M, U. New Mexico, Michigan, and U. Hawaii. Of the graduates of the MARC Honors Undergraduate Program, a total of 83 percent have entered graduate or professional schools. Fifty percent are in graduate school and 33 percent are in professional schools.

The entire Program is carefully monitored by the staff and the Minority Access to Research Careers Review Committee with oversight by the National Advisory General Medical Sciences Council. Progress reports are given to those two bodies on a regular basis.

Responsiveness to National Needs

At a recent Council meeting, Dr. Geraldine Woods noted that, in the early days of the program, she and staff of NIGMS had found that many professors in minority schools were so involved in instruction that they could not do research; and that many young instructors wanted to continue their education and obtain a doctoral degree, but had no financial aid. Since the initiation of the MARC Faculty Fellowships program, many of the fellowship recipients have returned to their institutions and become involved in the Honors Undergraduate Training Program and the Minority Biomedical Support Program, and many have obtained research grant support. In addition, the program has inspired the institutions to give the returned fellows release time, and to give them seed money for getting involved in research. Dr. Woods stressed the fact that, in her opinion, this program has had a very positive impact on the institutions involved.

Other Evidence of Program Efficiency

Since the MARC Program is, specifically, a training-oriented program, its efforts are directed toward increasing the numbers of ethnic minority individuals engaged in biomedical research and teaching. MARC endeavors supported by NIGMS are consistent with the Institute's overall mission and fields of primary scientific concern. The MARC program also collaborates with various other NIH Institutes in awarding support for programs in accord with their missions, and NIGMS views such collaboration as evidence of further support of the MARC Program activities. Such collaboration is in effect with the National Cancer Institute, National Heart, Lung, and Blood Institute, National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development, National Institute on Aging, National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Dental Research.

Studies To Assess Program Performance

Preliminary evaluation of the MARC Faculty Fellowship Program indicates that it has helped significantly in enabling faculty of minority institutions to obtain their Ph.D. degrees or postdoctoral training. Of the 150 fellows supported, 96 have completed the program so far. Of the 96, 73 have returned to their home institution and 14 have obtained positions at other minority institutions. Of the nine who did not return to a minority institution, four are currently in a research environment.

Major Issues

The National Institute of General Medical Sciences considers its MARC Program to be an Institute initiative and a direct response to a Congressional mandate in which that body has identified a significant national need for biomedical research training of minorities, and emphasized its intention to correct this deficiency by enacting legislation and appropriating funds fully supporting this effort.

Particular concern was expressed at the FY 1982 Appropriation Hearings in regard to the cutback in numbers of trainees and the proposed elimination of institutional allowances and indirect costs. Institutional allowances are really trainee-related costs and are comprised of funds for teaching personnel, consultants, equipment, and supplies. These costs have added up to more than 50 percent of the Institute's funding of minority institutions.

Major Barriers Relating to Program Performance

Since a major objective of the MARC Undergraduate Program is to increase the number of minority bioscientists pursuing research careers, one area of concern is that the data indicate that 33 percent of the graduates entered professional schools, and not graduate schools. This may reflect the increased recruiting efforts made by professional schools among minority graduates in response to other national mandates. If this is so, there are few remedies available to this Institute to reduce the substantial, existing career differences between science and medicine. The other concern is the 17 percent lost to science or medicine from among the Honors graduates. In recent progress reports to the National Advisory General Medical Sciences Council, it was noted that a number of students graduating from the Honors program may be reluctant to continue their education outside of a minority setting, are not aggressive in seeking out existing training opportunities, or have financial or family obligations that prevent them from continuing with high-quality graduate training.

In an effort to meet this problem, the MARC Program, in consultation with Institute staff, consultants, and the Council, has initiated a new component to the program--the MARC Predoctoral Fellowship. This newest part of the program was announced in January 1981 to provide support for research training leading to the Ph.D. degree in the biomedical sciences for selected students who are graduates of the MARC Honors Undergraduate Research Training Program. It is expected that such training will be conducted in graduate degree programs of the highest quality. Support is not available for individuals enrolled in medical or other professional schools, unless they are enrolled in an M.D.-Ph.D. program.

NIGMS

To date, 16 applications have been received from students in eight different institutions. Two of these students have since been offered support in regular NIGMS training grants. To date four awards have been made.

Documentation

"Minority Groups Among United States Doctoral-Level Scientists, Engineers, and Scholars, 1973," National Academy of Sciences, Washington, D.C., 1974.

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"Annual Report, Committee to Study National Needs for Biomedical and Behavioral Research Personnel," National Academy of Sciences, 1977.

"Science, Engineering, and Humanities Doctorates in The United States, 1979 Profile," National Academy of Sciences, National Research Council, Washington, D.C., 1980.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Director's Overview

The National Heart, Lung, and Blood Institute (NHLBI) has been issued the mandate to marshal the Nation's health resources into a comprehensive National Program to prevent and treat cardiovascular, pulmonary, and blood diseases and to improve utilization of our national blood resources. The challenge of this responsibility is great. For more than 50 years, heart and blood vessel diseases have been the major cause of death in this country. Over the years, the programs of the Institute have evolved as a coordinated effort to combat the devastating consequences of these diseases in terms of lowering morbidity and mortality and associated economic costs.

Magnitude of the Problem

Diseases of the heart, lung, and blood account for an inordinately large share of the sickness, death, and financial loss caused by illness, and the magnitude of NHLBI's responsibilities must be viewed in light of this burden. In 1979, of the ten leading causes of death in the United States, four fell within the purview of the NHLBI: diseases of the heart (first); cerebrovascular diseases (third); chronic obstructive lung diseases (fifth); and arteriosclerosis (ninth). These four major disease categories accounted for almost one million deaths, well over half of the total deaths in 1979.

Despite striking improvements over the last 20 years, diseases of the heart, blood vessels, lungs, and blood remain among the Nation's most serious health problems. Cardiovascular diseases constitute the leading cause of death for men over age 40 and for women beginning at age 60; and at least 40 million Americans have diseases of the heart and blood vessels. In addition, cardiovascular diseases caused over 51 percent of all deaths in 1979. Heart disease, in particular, often causes long periods of limited activity and accounts for more bed days than any other condition. The total economic burden of cardiovascular disorders is estimated to be in excess of $70 billion annually or over one-fifth of the total cost of illness in 1975, and accounted for 30 percent of all years of potential life lost to illness in 1975.

The social and economic burden of diseases of the lungs and respiratory system is equally severe. While these diseases cause fewer deaths than cardiovascular diseases, they kill earlier in life and account for more than 5 percent of all the potential years of life lost as a result of illness. In 1975, total economic costs for lung and related respiratory diseases accounted for over $19.1 billion. Since blood diseases so frequently strike during childhood, standard economic measures cannot fully reflect the loss or costs in terms of suffering and grief. These diseases, including the hemoglobinopathies, are the cause or complication of a variety of serious disorders.

Research Program Strategy and Goals

The National Program Plan addresses specific scientific goals and individual program areas. In order to meet these goals, the Institute utilizes a program strategy that lends direction and momentum to the National Program as a whole. The program strategy employed for each of the disease-related mandates of the NHLBI consists of an ordered sequence: acquisition of new knowledge, testing and evaluation of promising hypotheses, and dissemination of new and existing knowledge. To carry out this strategy, the three categorical Divisions have certain responsibilities and common objectives: increasing knowledge of normal and diseased organ systems through broad programs of basic and clinical research, clinical evaluation of research findings, and expediting the transfer of validated findings into medical practice; emphasizing programs of prevention; planning and coordinating research grant, contract, and training programs; evaluating existing activities and assessing future needs; and stimulating the health care communities to respond to identified needs.

FY 1981 Examples of Areas of Research Holding Great Promise for Future Progress

Calcium Channel Blocking Agents. Recent studies have shown that calcium ions play an important role in the cardiovascular system. They are involved in electrophysiologic processes, link excitation to muscular contraction, control energy storage and utilization, and constrict vascular smooth muscle in coronary and systemic arteries. A new group of pharmacologic agents that block the passage of calcium ions across cell membranes has recently been developed. These agents act during the slow inward current of cellular depolarization. The most extensive clinical experience has been obtained with four of these agents: verapamil, nifedipine, perhexiline, and diltiazem. Verapamil, for example, has profound electrophysiologic effects and is emerging as a valuable antiarrhythmic agent. All of these drugs have been shown to be of unique value in angina pectoris, cardiomyopathy, and hypertension. Further research on the role of calcium ions on the electrophysiologic processes and the influence of these drugs on the heart will have tremendous impact on cardiovascular medicine.

Percutaneous Transluminal Coronary Angioplasty (PTCA). The dilation of coronary arteries by a balloon-tipped catheter passed through the blood vessels to the site of obstruction represents a potential alternative to bypass surgery in approximately 5 percent of surgical candidates. This procedure could possibly lead to a less hazardous and less expensive method of treating such patients. Since experience with the technique is limited and its long-term benefits still need to be assessed, NHLBI has established a registry to facilitate further evaluation of this potential alternative to open heart surgery. Initial data indicate that in patients meeting the criteria established at a NHLBI-sponsored workshop (e.g., single vessel disease) that morbidity and mortality during the procedure are acceptably low and that one-year followups show high levels of arterial patency. A workshop to review progress will be held in June.

New Understanding of Genetic Predisposition to Emphysema. Some patients with emphysema possess a genetic defect resulting in the production of aberrant forms of the antiprotease alpha-1-antitrypsin (A1AT), of which 24 variants have now been identified. New methods of purification make it possible to isolate A1AT variants from 50 ml of serum in about 36 hours. Since antiproteases such as A1AT constitute the main line of defense against breakdown of lung proteins, the isolation and purification of genetic variants will advance understanding of the delicate imbalance between protease and antiprotease activity that develops in individuals with a genetic predisposition to emphysema. Future research will include clinical investigation of the effect of A1AT replacement in patients homozygous for A1AT deficiency, the development of synthetic protease inhibitors,and continued basic research on the basic physiologic and biochemical mechanisms.

Screening Blood Donors for Non-A, Non-B Hepatitis (NANB). Donor blood containing elevated levels of the liver enzyme alanine amino-transferase (ALT) carries a high risk of infectivity for NANB hepatitis. Screening donor samples for ALT may be useful as an intermediary measure for reducing the incidence of post-transfusion hepatitis, until such time as the viral agent(s) can be isolated.

Hypertension. The results of the Hypertension Detection and Follow-up Program (HDFP) randomized, controlled trial showed that systematic antihypertensive management at the HDFP clinical centers (stepped care) resulted in a 16.9 percent reduction in five-year mortality compared with the referred care group who received their treatment from usual sources of care in the community. In addition, for the *mild* hypertensives, the stepped care group experienced a 20.3 percent reduction in mortality compared with the referred care group. This study demonstrates that the systemic, effective treatment of *mild* hypertension is important in reducing premature deaths. The study provides the first scientific proof of the benefit of treating this group of patients, numbering approximately 25 million Americans. The results of this trial and the high levels of adherence among stepped care patients have broad implications for who should receive treatment and how they should be cared for and highlights the need for basic research into the cause of hypertension. The NHLBI will sponsor a workshop to discuss the implications of HDFP for health research and health care.

Noninvasive Diagnosis of Heart Disease. Instrumentation for the noninvasive diagnosis of heart disease is undergoing a rapid evolution. Echocardiography is being refined to provide cross-sectional images of the working heart. Specific radionuclides have been developed which selectively infiltrate ischemic muscle during the course of myocardial infarction. Computer-assisted instrumentation for noninvasive diagnosis offers the prospect of increasing accuracy and safety in the diagnosis, monitoring of treatment, and improved information of pathophysiology of many forms of heart disease.

Platelet-Active Drugs. Initiated in 1975, the Aspirin Myocardial Infarction Study (AMIS) was a randomized, double-blind, placebo-controlled clinical trial involving 4,524 patients recruited at 30 clinical centers. The incidence of nonfatal myocardial infarction in the group taking aspirin was not significantly different than controls, but there was a higher incidence of side effects, primarily gastrointestinal. The findings of AMIS differ from those of six other aspirin trials in post-MI patients, all of which have shown positive but nonconclusive results favoring the use of aspirin. This work has led to increased interest in the value of platelet-active drugs in the secondary prevention of coronary heart disease. Continued research investigating time of initiation of therapy, comparing various platelet-active compounds, and dosage schedules may lead to an appropriate preventive strategy in coronary heart disease.

Regulation of Cholesterol Metabolism. The esterification of plasma cholesterol, transfer of cholesterol esters, and the regulation of plasma cholesterol metabolism have been shown to be properties of a cholesterol ester transfer complex of unique composition. The complex consists of lecithin cholesterol acyl transferase (LCAT), apoprotein A-1, and the cholesterol ester transfer protein (apo-D) in a molar ratio of 1:1:2. The complex represents the whole of the plasma cholesterol-esterifying enzyme LCAT. This research represents a significant advance in our understanding of the regulation of cholesterol metabolism.

Primary Sequence of Human Fibrinogen. Very recently, the last amino acids of the primary sequence of human fibrinogen have been mapped, representing the successful culmination of ten years' work. Almost 20,000 separate analyses were required for the molecule, which contains 2,964 amino acid residues. A wealth of information is provided by this sequence, including the exact location of cross-link sites and cleavage points involved in fibrinogenolysis. This detailed map has allowed the construction of a three-dimensional model for the conformation of human fibrinogen. The prospect of a complete understanding of the chemistry of blood coagulation is brought much closer by this new knowledge, leading inevitably to more precise and effective pharmacological intervention in the prevention and management of thrombosis and clotting disorders.

Arteriosclerosis. In October 1978, the NHLBI established a working group to undertake a broad assessment of arteriosclerosis, from its basic etiology and pathophysiology to the prevention, diagnosis, treatment, and rehabilitation of its clinical sequelae. In summer 1981, the working group will complete a two-volume report containing conclusions and recommendations for future research opportunities in an attempt to understand arteriosclerosis and to prevent, or at least control, its dreadful consequences. Areas holding the greatest promise for future research include the study of basic mechanisms contributing to the etiology and progression of the condition; further development of sophisticated noninvasive technology such as echocardiography, radionuclide imaging, and CAT scanning, etc., to provide for early detection of atherosclerotic plaques; and epidemiological studies designed to determine the precise links between each of the established risk factors and the pathogenesis of the disease.

Evaluation Studies

The five advisory committees of the NHLBI evaluate program activity in their respective areas on a yearly basis. In addition, the Institute will be conducting a major program evaluation (RFP HO-81-4) which will assess the last ten years of progress and provide the major basis for choices and initiatives for the next five-year period from FY 1983-87. These mechanisms of evaluation, where appropriate, provide the rationale for the changes and priorities which are indicated below.

FY 1982 Major Program Changes

Research Grants

Research Projects

- An overall decrease in research projects (2,224 in FY 1981 to 2,173 in FY 1982).

This is based on the sum of:

- An increase in competing projects (644 in FY 1981 to 759 in FY 1982).

- A decrease in noncompeting projects (1,580 in FY 1981 to 1,414 in FY 1982). In FY 1979 the Institute had a peak of 942 competing projects, many of which will be terminating in FY 1982.

Research Centers

- Open recompetition of Arteriosclerosis, Chronic Airways Diseases, Fibrotic and Immunologic Interstitial Diseases, Pediatric Pulmonary Diseases, and Pulmonary Vascular Diseases Specialized Centers of Research. The overall number of centers will remain unchanged (59).

Research Career Programs

- Constant level of support will be maintained (329 awards in 1981, 329 awards in 1982).

- This includes a recompetition of:

  (1) Preventive Cardiology Academic Awards.

  (2) Pulmonary Academic Awards.

Training

- Total number of full time equivalents (FTEs) remains the same as FY 1981 (1,516).

Research and Development Contracts

- Decrease in support of research contracts from FY 1981 to FY 1982; Neonatal RDS ended in FY 1981.

- Program expansion: Pilot phase to Phase I. As recommended by Task Force on Epidemiology as first priority, Community Surveillance System for Cardiovascular and Other Chronic Diseases: to establish a surveillance system to monitor, in 10 geographically circumscribed communities representing regionally different parts of the United States, possible recurrent myocardial infarctions, and cardiac deaths over time.

Intramural Research

- Program unchanged; slight increase in cost to accommodate inflation.

FY 1983 Major Program Changes

Research Grants

Research Projects

- Increase in noncompeting projects (1,414 in FY 1982 to 1,566 in FY 1983).

- Increase in competing projects (759 in FY 1982 to 820 in FY 1983).

  This results in:

  An overall increase in research projects (2,173 in FY 1982 to 2,386 in FY 1983).

- New initiatives:

  The following RFAs (requests for applications) would be released:

  --Cholesterol and Non-CVD Mortality. To assess the possible relationship between very low blood cholesterol levels (180 md/dl) and increased mortality from various forms of cancer.

  --Transport of Macromolecules by the Respiratory System. To investigate the movement of macromolecules such as antigens, antibodies, enzymes, and vasoactive substances across membranes in the normal respiratory system and determine if regional differences exist within the lung with regard to these movements and the factors that regulate them.

  --Perfluorochemicals (Blood Substitutes) Research. The objective is to foster basic and applied physiological research using available perfluorochemical blood substitutes as research tools.

--Longitudinal Studies of Coronary Heart Disease Risk Factors In the Young. To measure changes in risk factors (e.g., blood lipids and lipoproteins, blood pressure, adiposity, blood sugar) that have been associated with the development of coronary heart disease in cohorts of males and females newborn to 30 years of age.

--Structure and Function of Lung Development in Response to Maternal Nutrition. To study the utilization by the fetal and neonatal lung of key substrates from maternal nutrition and to correlate the morphological, physiological, and biochemical characteristics of the developing lung with exposure to (or lack of) these substrates.

--Cardiovascular Disease (CVD) Nutrition Research Unit for the Study of Nutrition and Heart and Vascular Disease. To establish close interaction and collaboration between investigators in CVD and nutrition, to offer a broad range of research training activities oriented toward human nutrition in health and disease.

--Study of the Defense Mechanisms of the Developing Respiratory System. To achieve a better understanding of the temporal development of defense mechanisms in the fetal and neonatal respiratory system such as phagocytosis, mucociliary transport, and metabolic conversions, and of the ability of the developing lung to respond to foreign substances.

--Blood Material Interactions. To continue fundamental studies on the interactions between blood and various materials that are candidates for prosthetic and invasive devices.

--Chronic Obstructive Pulmonary Disease (COPD) and Lung Extracellular Matrix Interaction. It is now believed that COPD is produced by an imbalance in the levels of functional alpha-1-antitrypsin and elastase leading to an accelerated degradation of lung elastin. However, very little is known about the effects of changes in the interactions between the components of the extracellular matrix on the disease and repair processes. The objective of this program is to look at the effect of lung matrix interactions on COPD. Investigations at biochemical and/or cellular level, but excluding exclusively morphometric studies, would be encouraged.

--Platelet and Leukocyte Immunology. A study of new serological markers in platelets and granulocytes.

--Obesity and LDL Relationship. To stimulate investigator-initiated research to clarify a relationship between obesity and the levels and metabolism of LDL and other lipoproteins.

Research Centers

- Additional funds are planned to initiate six new SCORs (Specialized Centers of Research) on Arteriosclerosis in the Young: These centers will combine research on the prevention and treatment of congenital and rheumatic heart disease with research on the precursors of heart and vascular disease in the adult.

Research Career Programs

- An additional 31 awards above the FY 1982 level, including expansion of the Clinical Investigation Awards program and the Preventive Cardiology Academic Awards program.

Training

- An increase of 79 trainees, to partially alleviate certain training shortage areas, particularly among M.D. researchers.

Research and Development Contracts

- Full funding of the ongoing clinical trial program.

- New Initiatives:

  --Systolic Hypertension in the Elderly Program (SHEP). Determine whether treatment of isolated systolic hypertension in 4,200 patients 60 years of age or older randomized to treatment and control will reduce the incidence of stroke. Secondary aims are to evaluate the effect of treatment on total morbidity, fatal and nonfatal myocardial infarction, congestive heart failure and renal insufficiency, and cognitive impairment and psychiatric morbidity.

  --Platelet Active Drugs and Myocardial Infarction. Recent clinical trials indicate that the first year following myocardial infarction and in particular, the first three months, may be a critical period in which administration of platelet active drugs may be most effective in prevention of sudden death. This trial will evaluate the effect of various platelet active drugs (aspirin, Persantin, Anturane) on mortality and morbidity during the first three months following myocardial infarction.

  --Nutrition and Lifestyle Education Programs. In conjunction with the Institute's highly successful National High Blood Pressure Education Program, the Institute will begin a new program to disseminate to the public the results of the Multiple Risk Factor Intervention Trial (MRFIT) and the Lipid Research Clinics (LRC) trial, both of which will be reaching completion in FY 1983.

Intramural Research

- Increased above FY 1982 to provide for inflation.

Potential Impact of Program Changes on Three Year Period (1983-1985)

For NHLBI to carry out its mandated responsibilities, Institute resources must increase each year to match both inflation and advances in the sophistication of scientific technologies. In the current atmosphere of responsible Federal fiscal restraint, the inability of NHLBI to fund all meritorious research projects requires that program planning and implementation activities carefully deliberate among competing priorities. With this perspective, the Institute identified the new initiatives presented for FY 1983 based on a critical review of the state of the science, future research opportunities, and specific estimates of resources needed to support both ongoing commitments and new initiatives.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Heart, Lung, and Blood Institute

DATE: MAR 5 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It is encouraging to note the advances that have been made in the understanding of cardiovascular, pulmonary and blood diseases, as well as the dramatic reduction in heart attack and stroke deaths. Programs such as your disease prevention and health promotion at the worksite are examples of a new focus on collaboration with industry which can operate well within the constraints imposed by an austere budget, and may serve as models for future efforts. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

Cardiovascular disease remains the leading cause of death in the United States, and chronic obstructive pulmonary disease is the most rapidly increasing of the top 10 causes of death. However, during the past decade there has been a decline of 25 percent in the number of heart attack deaths and a 37 percent drop in the number of stroke deaths.

Diseases of the heart and blood vessels account for more than 50 percent of all deaths in the Nation each year. There are over 600,000 deaths from heart attacks every year and 175,000 stroke deaths. Chronic obstructive pulmonary diseases, emphysema, and bronchitis accounted for over 50,000 deaths last year. While deaths attributed to blood diseases are considerably fewer in number, blood related problems impact upon all processes of the body. In terms of economic costs, the diseases addressed by the NHLBI total more than $72 billion annually, with diseases of the heart and blood vessels representing over $50 billion.

Impact of Stabilization

- Since 1975, the Institute has accorded highest priority to the support of investigator-initiated research project grants, and during the 1970s was able to award a fairly stable share of the total number of NIH competing awards. This share declined substantially in 1980, and the outlook for 1981 and 1982 is not much better.

- Competing research project grants fell dramatically in 1980 from the 1979 level, and although some increases in the number of funded competing project grants are planned in 1981 and again in 1982, the total of competing grants will remain well below the 1977, 1978, and 1979 levels. Total 1980--competing and non-competing--research project grants will remain below the 1979 level, and this trend will continue each year for 1981 and 1982.

- The application of the stabilization initiative, coupled with a relative decline in total funding, is causing serious imbalances. The most severe impact will be felt in clinical trials and targeted research, funded under the contract mechanism, where no new efforts can be implemented in 1980-82. Research and development contracts have decreased in number and in funds expended, and will continue to do so throughout this period. The contract mechanism is best suited to fund clinical trials, and rapid advances in research and developments in cardiovascular and pulmonary treatment techniques necessitate clinical evaluation at a time when no new contracts can be awarded.

- The number of research centers will remain constant without any room for expansion during 1981 and 1982, although the need for new specialized centers in pediatric cardiovascular disease is well documented.

- Research career programs will grow modestly in number in the 1979-82 period, but will remain well below needed levels. The Clinical Investigator Award and Preventive Cardiology Academic Award have begun at a reduced pace and only at the cost of the ongoing Research Career Development Award Program.

- The total number of training awards increased in 1980 from the 1979 level, and is projected to stabilize in 1981 and 1982 at the 1980 level. Competing training awards rose sharply in 1980 (in part, because the continuing resolution funding level in 1979 allowed few new awards); however, fewer competing awards will be funded in 1981 and 1982.

- Intramural research levels will remain constant.

Clinical Trials

Due to budgetary restrictions, no clinical trials have been initiated since 1979. Given the state of scientific progress in the areas within the scope of NHLBI programs, however, clinical trials should be expanded in order to bridge the gap between research developments and achievements in health care practices.

A number of clinical trials have been suggested by the NHLBI advisory boards, and several areas are ripe for clinical investigation. Several high-priority trials which could be undertaken if resources were available include Platelet Active Drugs and Myocardial Infarction, Systolic Hypertension in the Elderly, Assessment of the Clinical Utility of Percutaneous Transluminal Coronary Angioplasty, and Prevention of Pulmonary Emphysema in Patients with Alpha-1-Antitrypsin Deficiency.

Collaboration With Industry

The NHLBI has developed collaborative efforts with the private sector in the areas of health promotion and disease prevention at the worksite. Providing expertise and technical assistance, but using private resources, NHLBI has worked with employers and unions to develop worksite programs, particularly in hypertension control, and has worked with insurance companies on programs for their own employees and for policy holders. The Institute has also developed seminars on cardiovascular health at the worksite for the American Occupational Medical Association and the American Association for Occupational Health Nurses, to assist individual members in establishing programs at their respective workplaces. Followup measurements have shown reduced absenteeism and increased productivity following the initiation of the cooperative health programs.

Selected Research Activities and Opportunities

- The primary sequence of human fibrinogen has been mapped, allowing construction of a three-dimensional model of the conformation of the protein molecule. This represents the successful culmination of ten years' work and brings closer the complete understanding of blood coagulation and the possibility of better treatments for thrombosis and clotting disorders.

- The Hypertension Detection and Follow-up Program has demonstrated a significant reduction in five-year mortality in an experimental patient group who received systematic hypertension management as opposed to the controls, who were referred to usual sources of care. In mild hypertensives, results were even more pronounced. This study demonstrated that the systematic, effective treatment of hypertension, especially mild hypertension, is effective in reducing premature deaths. It provides the first proof of the benefit of treating mild hypertensives and has broad implications for the treatment of hypertensives throughout the U.S. health care system.

- Calcium channel-blocking agents have been found to have profound electrophysiologic effects and are being tested as antiarrhythmic and muscle relaxing agents. Their role in coronary artery spasm, hypertension, and hypertrophic cardiomyopathy is also being evaluated. Further investigation of the role of calcium ions on muscle contractility and electrophysiologic processes appears to hold great promise in cardiovascular medicine.

- Instrumentation for noninvasive diagnosis of heart disease is undergoing a rapid evolution. Computer-assisted instrumentation for noninvasive diagnosis offers the prospect of increasing accuracy and safety in diagnosis, treatment monitoring, and improved information regarding the pathophysiology of heart diseases.

- The dilation of blocked coronary arteries with a balloon-tipped catheter passed through the blood vessel represents a possible alternative to bypass surgery in 5 percent of potential surgery candidates. A workshop to review progress with this technique will be held by NHLBI in June 1981.

- A correspondence between high levels of the liver enzyme alanine aminotransferase (ALT) in donor blood and infection with Non-A, Non-B hepatitis has been found. Screening for ALT may be used until the viral agent itself can be identified, in an effort to reduce post-transfusion hepatitis.

- Certain emphysema patients are found to possess a genetic defect which causes them to produce aberrant forms of antiprotease alpha-1-antitrypsin (A1AT). Antiproteases such as A1AT normally prevent the breakdown of lung proteins. Further research will include the evaluation of A1AT replacement in patients with the defect, and studies of protease inhibitors related to the processes occurring in all patients with emphysema.

Black Health Providers Task Force

In its FY 1981 report, the House Appropriations Committee called on the Department to prepare an initiative in response to the recommendations of the Black Health Providers Task Force on High Blood Pressure Education and Control. The report recommended that NHLBI be commended for sponsoring the task force and for its positive response to the task force recommendations. The Institute was requested to prepare the Departmental response, and has done so by listing Institute activities in response to the task force and suggesting other studies or activities that could be undertaken by other Departmental components.

Many of the issues addressed, however, are outside the purview of the Institute; and although the Institute exercises a coordinating role in this area through its National High Blood Pressure Education Program and its Interagency Technical Committee, it cannot assign activities to other agencies, such as Health Care Financing Administration (HCFA) or the Veterans Administration (VA), which received the specific attention of the task force. The NIH concurs with the position of the House Appropriations Committee that many of the needed actions are outside of the purview of the Institute and must be addressed by HHS or other specific agencies.

Research and Demonstration Centers

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423) called for the development of centers for basic and clinical cardiovascular and pulmonary research. In 1975, three "National Research and Demonstration Centers" were established, but further expansion was limited by lack of funds. An advisory council working group has completed a review of the operation of the three centers and concluded that the centers are not operating under an optimally designed profile. At this time, each center has two years of remaining fund commitment. A new profile for Research and Demonstration Centers is under design by a working group of Institute staff and council members. The preferred alternative to the present concept would be a two-phase approach that will result in the establishment of a capability for demonstration and education research activities in the community, followed by core grants to institutions with successful basic research, clinical investigations, and demonstration and education research activities capable of meeting the goals of a new National Research and Demonstration Center.

Action Items

Please proceed with the selection of a special committee to evaluate the ethical and technical issues related to the development of the artificial human heart. The committee will not be expected to devise specific research recommendations, but should provide the Director, NIH, with an overview and possible positions.

It would be very useful to have, before the Appropriation hearings, a list of high-priority clinical trials which the NIH could undertake but lacks resources to do so. I have asked Dr. Robert Gordon, with the assistance of the NIH Clinical Trials Committee, to develop this information.

Collaborative Efforts With the Private Sector

Statement of Issue

The Department and the National Institutes of Health, in particular, have often been urged to develop more collaborative efforts with the private sector. According to press reports, cooperative agreements have been suggested as desirable by members of the incoming Administration and were alluded to in the Republican Party platform as well. It is anticipated that Congressional committee members will raise this issue during authorization and appropriation hearings and may ask what sort of catalyst role NIH plays or intends to play in this area.

Discussion of Issue

NHLBI has had some success in this area and has examples to illustrate how NIH knowledge and technical assistance coupled with private resources can indeed result in mutual benefit as well as improved health for our citizens. One particular area of growing activity in this regard is health promotion and disease prevention at the worksite. Acting as a catalyst, NHLBI has assisted such groups as General Motors, United Steel Workers of America, Boeing Aircraft, and Bethlehem Steel in developing worksite programs, particularly in the area of high blood pressure control. NHLBI has also developed and implemented seminars on cardiovascular health at the work-site for both the American Occupational Medical Association and the American Association for Occupational Health Nurses to assist these groups in initiating projects within their respective companies. The Institute has also launched cooperative efforts with several insurance companies, e.g., Travelers, Metropolitan, and Blue Cross/Blue Shield, to assist in the development, expansion and/or evaluation of disease prevention/health promotion programs at their own worksites and among group subscribers. NHLBI is also currently acting as catalyst to bring insurance companies together to promote the policy of reduced premiums for hypertensives who bring their blood pressures under control. This may serve as an important incentive for hypertensives to adhere to their treatment programs.

Alternatives and/or Suggested Position

Recent years have evidenced increasing involvement by private industry in areas of disease prevention and health promotion. For business, these activities have the attraction of potential cost benefits via less absenteeism, sickness-related drops in productivity, and health benefits expenditures. For NIH, industry provides a cost-efficient channel through which the fruits of basic and applied research can be transmitted for the good of the public health. It is suggested that NIH's position reflect an acute awareness of the benefits resulting from private industry's involvement in disease prevention/health promotion and that NIH intends to explore with industry additional areas where public benefit may result from collaborative effort.

Research and Demonstration Centers

Statement of Issue

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423) called upon the Director, NHLBI, to provide for the development of ". . . new centers for basic and clinical research into, training in, and demonstration of, advanced diagnostic, prevention and treatment methods . . ." for heart, lung, and blood diseases. In 1975, three "National Research and Demonstration Centers" (one each in heart, lung, and blood) were initiated by the Institute. These centers were broad in scope, encompassing a wide range of activities in a continuum from fundamental research to education (public and professional) and demonstrations of innovations in health care delivery and community service. A Council Working Group recently reviewed the NRDC Centers and concluded that while current centers are useful, the present profile is not advantageous nor would the entire concept be made any more acceptable simply by expansion of the number of centers. Consequently, a working group of NHLBI staff and Council members has initiated the planning and development of a new profile of NHLBI Research and Development Centers to be released in February 1981.

Discussion of Issue

There is a clear mandate from the Congress, stated as early as 1972 and renewed with each reauthorization, that NHLBI should provide for research and demonstration centers. However, from the beginning, funding for these centers has been limited by the competing Institute priorities of provision of support for investigator-initiated research and training opportunities. Consequently only three centers have been awarded. The heart and vascular disease center is at Baylor College of Medicine in Houston; the lung disease center is at the University of Vermont in Burlington; and the blood resources center is at the Puget Sound Blood Center in Seattle.

In 1977, after considerable discussion with the Advisory Council, the Institute issued a program announcement and guidelines for renewal support for the three centers. This competition was limited to the three centers that had been established and funded. Each center site was visited and thoroughly reviewed. The results were brought to the Advisory Council in September 1978. After careful deliberation the Council recommended three additional years of support. At this time each center is in its sixth year of support with two additional years of commitment.

The recent Advisory Council Working Group appointed by the Director, NHLBI, in February 1979, examined the impact and concept of these centers. The group stated:

> "At a time that there are identifiable centers of laboratory, research, clinical research, and prevention, education research, all of quality permitting peer acknowledgement and funding for their own activities, there then should be encouragement for such centers to interact within an administrative structure that will facilitate accomplishment of goals that extend beyond those of the three units operating independently. The institute should offer funding for the administrative activities of such a

center and designate it as an NRDC. Funding of the basic activities of the three components, however, should continue through the peer system unique to each of the three general systems."

Alternatives and/or Suggested Position

A second working group of NHLBI staff and Advisory Council members has been working over the past three months to design a new profile for R&D Centers in compliance with the Advisory Council's recommendation. The preferred alternative is through a two-phase approach. Phase I is the initiation of a Demonstration and Education capability by the community through a solicitation via an RFA for research grants. Thus, a capability for demonstration and education activities would be established in the community. Phase II would follow with an RFA for core grants for institutions that have successful basic research, clinical investigations, and demonstration and education activities to fulfill the expectations and goals of a National Research and Demonstration Center. The laboratory-based and clinical research efforts would be supported by successful competition through the various ongoing peer review systems available at NIH. Thus, the two-phase Center concept would support centers which would be amalgamated into a new National Research and Demonstration Center Profile.

Black Health Providers Task Force

Statement of Issue

In its FY 1981 report, the House Appropriations Committee called on the Department to prepare an initiative in response to the recommendations of the Black Health Providers Task Force on High Blood Pressure Education and Control. The report recommended that NHLBI be commended for sponsoring the task force and for its positive response to the task force recommendations. It noted, however, that many issues were outside the purview of NHLBI and a Department-wide initiative should be developed utilizing task force recommendations and including legislative and budgetary proposals, if necessary.

Discussion of Issue

NHLBI was requested to prepare a draft of the Departmental response. It did so, but noted that lack of time precluded sufficient interface with many of the HHS and other Federal programs to seek their input and develop proposals related to their areas of concern. Consequently, NHLBI prepared a draft response listing NHLBI activities in response to the task force and suggesting other studies or activities that might be undertaken by other Departmental components. It was also suggested that these proposed activities be pursued by OS or OASH with affected program components. Although NHLBI exercises a coordinating role through the National High Blood Pressure Education Program (NHBPEP) and the NHLBI Interagency Technical Committee, the Institute is not in a position to assign activities to such agencies as HCFA or the VA, both of which received specific attention by the task force.

Alternatives and/or Suggested Position

Among the NHLBI responses to the task force recommendations to date are: wide-scale distribution of the report itself; a demonstration program in conjunction with Health Services Administration (HSA), in five minority communities; the preparation of monographs for specific provider groups; the convening of a working group on diffusion strategies for minority populations; and invitation to task force provider groups to join the Coordinating Committee of the NHBPEP. Many recommendations represented areas in which the Institute was already active. It is suggested that the position of NIH reflect an appreciation for the important work of the task force to take advantage of related opportunities as they arise. While acknowledging the established coordinating role of NHLBI in high blood pressure control activities, NIH should also reinforce the House Appropriations Committee in its declaration that many of the recommendations are outside the purview of NHLBI and must be addressed by the Department and/or specific agencies which have the responsibility or mandate for developing pertinent budgetary or legislative proposals.

Clinical Trials

Statement of Issue

A strong clinical trial program is absolutely essential to the conduct of the National Heart, Blood Vessel, Lung, and Blood Program. The clinical trial is the key evaluation tool that bridges the validation gap between research developments and achievements of health practice. Yet the budget emphasis on research project grants posed by stabilization for the past three years has not allowed the Institute to begin any new trials. If current funding trends continue, critical needs for validation efforts cannot be undertaken with a concomitant loss to the Nation in both health status and economic terms.

Discussion of Issue

The trend over the past years toward support of research project grants is critical for the maintenance of a strong investigator-initiated research program essential to the generation of new knowledge. Yet this knowledge must be validated if it is to be applied effectively. Validation efforts, largely consisting of prospective randomized clinical trials, are a key portion of the NHLBI program. However, if present funding trends continue, emphasizing research project grants at the expense of the full NHLBI research program, the Institute will not be able to begin any of the new validation efforts so critically needed. During the past three years no new dollars have been provided to the contracts program beyond existing commitments. Moreover, the NHLBI extramural budget has not kept pace with the Institute's increased mandates and with inflation.

The problem is becoming increasingly critical. Under the current stabilization program the portion of the extramural budget devoted to research project grants (not including centers and training) will increase from 60 percent in 1979, to a projected 69 percent in 1983 at the current level. Concurrently, the contracts program (which includes all the major clinical trials) is projected to fall from some $98.1 million (or 22 percent of the extramural budget) in 1979, to $70.9 million (14 percent) in 1982, to only $45.0 million (9 percent) in 1983 at the current level. These figures reflect an inflexible budget position which does not allow any new validation efforts to be undertaken. (These changes are all the more severe since the NHLBI strategy from 1974 to 1979 has been to increase activities at the science base at the expense of validation and application. For example, between 1974 and 1979 research program grants rose from 48 percent of the extramural budget to 60 percent, while contracts fell from 28 percent to 22 percent.)

The need for new evaluation efforts is pressing. The following efforts have all been proposed for initiation but are awaiting sufficient funding before the Institute can move forward to, first, plan and, second, initiate the needed trials.

Proposed at the Current Services Level

Systolic Hypertension in the Elderly Program (SHEP). To determine whether treatment of isolated systolic hypertension in 4,200 patients 60 years of age or older randomized to treatment and control will reduce the incidence of stroke. Secondary aims are to evaluate the effect of treatment on total morbidity, fatal and nonfatal myocardial infarction, congestive heart failure and renal insufficiency, and cognitive impairment and psychiatric morbidity.

Platelet Active Drugs and Myocardial Infarction. Recent clinical trials indicate that the first year following myocardial infarction and in particular, the first three months may be a critical period in which administration of platelet active drugs may be most effective in prevention of sudden death. This trial will evaluate the effect of various platelet active drugs (aspirin, Persantin, Anturane) on mortality and morbidity during the first three months following myocardial infarction.

Prevention of Pulmonary Emphysema in Patients with Alpha-1-Anti-Trypsin Deficiency. To develop and test synthetic low molecular weight elastase inhibitors for the treatment of patients with the genetic deficiency of alpha-1 antitrypsin.

Proposed at the Intermediate Level

Percutaneous Transluminal Coronary Angioplasty (PTCA). To evaluate the effect on morbidity and mortality of PTCA therapy on patients with advanced coronary artery disease. PTCA may be a feasible, less costly alternative to coronary artery surgery and a more effective therapy than nonsurgical management.

Validation of Noninvasive Assessment of Large Vessel Atherosclerosis. The progress that has been made in noninvasive techniques to assess large vessel atherosclerosis could significantly enhance the likelihood of safe, inexpensive, early detection of progressive atherosclerosis. This trial will validate the new techniques against the existing invasive methods, a necessary step before widespread application of the techniques.

Effect of Dietary Modification in Blood Pressure Control. To determine whether an intervention of sodium intake restriction plus potassium intake elevation and an intervention of weight loss reduces the need for drug therapy. Approximately 700 male and female currently controlled hypertensives and 240 patients with uncontrolled blood pressure will be included in the study.

Longitudinal Studies of Coronary Heart Disease Risk Factors in the Young. To measure changes in risk factors (e.g., blood lipids and lipoproteins, blood pressure, adiposity, blood sugar) that have been associated with the development of coronary heart disease in cohorts of males and females, newborn to 30 years of age.

Proposed at the Request Level

Prevention of Sudden Death in High Risk Populations. To evaluate detection strategies for individuals at high risk for sudden cardiac death and to evaluate device- and drug-oriented preventive regimens. The trial will include the evaluation of implantable defibrillation devices as well as antiarrhythmic drugs.

Clinical Efficacy of Human Serum Albumin. To establish the extent of effectiveness of serum albumin used in the treatment of patients.

Feasibility of the Development of Markers To Be Used as Adherence Measures in Clinical Trials of Pharmacologic Agents. To develop safe, stable, and noninterfering, nonradioactive substances that can be added to pharmacologic agents which may be used in clinical drug trials or therapeutic intervention trials to assess patient adherence to the drug regimen.

Modified Hemoglobin. To test various forms of modified hemoglobin as blood replacement preparations.

Sterile Connecting Device for Blood Bags. To demonstrate and evaluate the most promising existing types of docking devices in terms of potential uses, acceptability to the user communities, cost-effectiveness, and safety and efficacy.

Effectiveness and Long-Term Results of Bronchial Drainage. To (1) evaluate the different bronchial drainage procedures during short intervals of time, and (2) examine the long-term consequences of drainage procedures. The determination of the effectiveness of these procedures would be evaluated with objective criteria including spirometry, and arterial blood gas and sputum volume determinations before and after treatment and over an appropriate time interval.

None of the above studies can be started at the current level. As a result, NHLBI is unable to carry out its full mandate: the increase of the knowledge base of heart, lung, and blood diseases and blood resources, and the validation and dissemination of the knowledge to the medical and lay public.

Alternatives and/or Suggested Position

The need and opportunity for clinical validation grows in direct proportion to our research advances. The needed trials listed above testify to the critical inflexibility of the current NHLBI fiscal position. Validation efforts must not decrease at the expense of maintenance of the knowledge base. NHLBI requires sufficient resources to undertake its full mandate commensurate with the state of science and health care needs. An adequate and flexible budget is the only solution to a growing crisis in the NHLBI clinical trial program.

Arteriosclerosis

Statement of Issue

In October 1978, the NHLBI established a working group to undertake a broad assessment of arteriosclerosis, from its basic etiology and pathophysiology to the prevention, diagnosis, treatment, and rehabilitation of its clinical sequelae. This working group was appointed because the recommendations of a similar group appointed a decade earlier had proved useful and had had a large impact on the direction of the research programs in arteriosclerotic disease in the ensuing eight years. For each element in this broad field of research the working group was asked to:

- Assess progress and present understanding;
- Highlight unresolved problems;
- Emphasize opportunities for research, with particular attention to preventive measures, therapies, and technologies that may be ready for clinical trials or application.

In February 1981, the working group will complete a two volume report Arteriosclerosis-1981, Progress and Prospects with conclusions and recommendations for future research opportunities in our attempt to understand arteriosclerosis and prevent or at least control its dreadful sequelea.

Discussion of Issue

Arteriosclerosis, in its most common form as atherosclerosis, is the major killer process of the 20th century. In most cases of coronary artery and cerebrovascular disease as well as in aortic aneurysm and peripheral vascular disease, severe atherosclerosis is the underlying pathological condition. In 1978, atherosclerosis caused 873,000 deaths in the United States, almost half of all deaths, at an estimated cost in health expenditures and lost productivity of over $39 billion.

In the past decade significant strides have been made in understanding basic mechanisms contributing to the etiology and progression of atherosclerosis. New animal models including nonhuman primates are now being studied, since physiological processes in these animals are likely to resemble those in man. New insights have been achieved through studies of the metabolism and interaction of plasma lipoproteins, apoproteins, enzymes, macrophages, and platelets with the endothelial cells and media of the vessel wall. The potential role of platelet and endothelial derived factors like thromboxane and prostacycline on vessel wall contractility and thrombus open up new avenues for research.

Early detection of atherosclerotic plaques in blood vessels, especially in those supplying the heart and brain, and early and improved diagnosis of the extent and nature of myocardial and cerebral ischemia and damage, have greatly improved, thanks to sophisticated noninvasive technology such as echocardiography, radionuclide imaging, computerized axial tomography (CAT scanning), etc. Significant progress has been made in the application of bypass surgery for atherosclerotic disease.

Epidemiological studies have shown that there are a number of risk factors for arteriosclerosis, and through the NHLBI programs on prevention and control, dissemination of information has led to a heightened public perception of ways to eliminate or reduce these risk factors so as to prevent or at least delay atherosclerotic diseases.

Alternatives and/or Suggested Position

Clearly, the recommendations contained in this 1981 report indicate that much additional research, both basic and clinical, is needed before atherosclerosis is to be brought under control.

Because of the great strides made in the past decade in understanding the fundamental causes of arteriosclerosis, NHLBI is firmly committed to the pursuit of more in-depth clues of basic mechanisms of atherosclerotic plaque formation. To accomplish this, bright, young investigators must be attracted to carry out these kinds of studies and continued support of promising new leads in basic knowledge is needed. Clinical trials are also paramount to evaluating methods in diagnosis, prevention, or treatment of the disease, although it is acknowledged that they are expensive, difficult to organize and administer, and time consuming.

Noninvasive methods to diagnose atherosclerotic lesions have been developed in the past decade, and two of these, ultrasound imaging with B-mode or Doppler systems, are ready for clinical application to evaluate them before their use becomes widespread.

Treatment of coronary artery and peripheral vascular diseases by percutaneous transluminal angioplasty appears to have great promise but must be evaluated as to its immediate and long-term effects before it can become an accepted therapeutic modality.

Epidemiological studies have been invaluable in identifying a host of risk factors for atherosclerotic disease, including diet, smoking, hypercholesterolemia, hypertension, age, sex, and genetics. However, the precise links between each of these risk factors and the pathogenesis of arteriosclerosis remains to be elucidated; and further population research is essential.

Senior Executive Service

Contract Comparability

Statement of Issue. Evaluation of both Senior Executive Service (SES) and merit pay employees involves comparing contracts covering a variety of different job descriptions and settings. Methods to facilitate comparison are critically needed if we are to achieve the promise of these new personnel compensation strategies.

Discussion of Issue. The SES and merit pay procedures hold the promise of rewarding individuals for the diligence, productivity, and quality of their work. The system hinges on comparisons of contract achievement ratings across a number of job classifications and work settings. While procedures have been set forth to develop contracts, these procedures were not tested to determine whether contracts and ratings would be comparable. For the system to be equitable it is critical to have sufficient time to assess the suitability of the contracts for future assessment and rating, and the feasibility of comparing the potential contract assessments. Even one year of an inequitable rating system will severely hurt employee morale and productivity.

Alternatives and/or Suggested Position. A careful study of both SES and merit pay contracts written to date is critically needed. Moreover, a trial run of assessment seems to be required before final assessments are made at the end of the year. It seems appropriate to form a committee to review contracts for their compatability and to supervise a trial run of contract assessment. Supervisors would then be able to grade employees based on hypothetical salary pools and see the results. The feedback should improve the system and, moreover, will assure all those participating that adequate planning and experience have been expended to make the system as effective as possible. Not to do so will damage even further a personnel system already inadequate to reward individuals for their efforts.

Recruitment

Statement of Issue. There are excessive delays and restraints on recruitment of members of the Senior Executive Service.

Discussion of Issue. Since members of the Senior Executive Service are our top program leaders, they are our most critical resource; their presence in the Institute for program direction is essential. However, there are built into the SES recruitment system many clearances and constraints that have added up to a year's delay in adding program leaders. For example, months are lost while waiting for permission to recruit for an SES position, even though the former incumbent was in SES. More time is lost, sometimes months, awaiting clearance on a search plan. Further delays ensue after a tentative selection is made by the Bureau/Institute/Division.

At this time there appears to be no attempt to change these procedures. Programs with responsibility for millions of health care dollars are forced to mark time for a year or more, while bundles of paper wend their way up through the Department for approval. The travesty is that these same bundles of paper, with slight but time-consuming variation, make more than one slow trip to the top before a final selection is approved. There appears to be a complete lack of awareness of the devastating effect this process has on recruitment and program performance. This is bureaucracy at its worst, where the process assumes all importance and the activity for which the process exists is lost sight of. This was not the intent of the Civil Service Reform Act.

Alternatives and/or Suggested Position. Alert the new PHS administration to the impact on our programs of the failure to adhere to the promises in the Civil Service Reform Act before the current procedures are accepted with little or no modification.

PROGRAM PERFORMANCE SUMMARY

HYPERTENSION RESEARCH

Program Description

Prevalence and Economic Costs

Hypertension--high blood pressure--is a leading cause of death and disease. Hypertension is the primary cause of tens of thousands of deaths in the United States each year and is believed to be the direct cause of hundreds of thousands of deaths from heart attacks and strokes (the first and third causes of death in the Nation). Hypertension is a silent killer: in its early stages it produces no symptoms that require medical attention. In its later stages, it results in major complications such as stroke, heart attack, heart failure, kidney failure, and, possibly, atherosclerosis. Hypertension has conservatively been estimated to cost the Nation over $8 billion a year in health care costs, lost productivity, and wages.

Although its prevalence rises steadily with age, hypertension also afflicts persons in the prime of their lives and in their most productive years. Nine out of 10 cases are "essential hypertension" (hypertension of unknown etiology) for which there is no known cure. It is more prevalent and also more severe in blacks than in whites. A 1971 to 1974 national survey estimated that 35 million persons in the United States, about 18 percent of the adult population, have definite hypertension (either a systolic blood pressure of 160 mm Hg or more or a diastolic blood pressure of at least 95 mm Hg). An additional 25 million Americans have so-called borderline hypertension, with systolic blood pressures between 140 and 160 mm Hg or diastolic blood pressures between 90 and 95 mm Hg. The survey also showed that 49 percent of the adult population with a hypertension problem were unaware of their disease, and of those who were aware, less than half were receiving adequate therapy. Once the disease is detected, however, it can usually be controlled. A recently concluded (November 1979) clinical trial, the Hypertension Detection and Follow-up Program (HDFP), has concluded that treatment effectively reduces the incidence of sequelae even in those with only "mild" hypertension, and suggests that about 60 million Americans have elevated blood pressures that warrant surveillance or intervention.

The Etiology of Hypertension

Hypertension results from a breakdown in the complex control system that maintains equilibrium between the constricting and dilating forces affecting the arterial walls. In hypertension, the normal level of balance is shifted so that the blood is circulated in the arteries under higher pressure. This increased pressure may damage the blood vessels and the heart. The several complex systems known to regulate blood pressure--humoral, neural, central, and peripheral--are under extensive investigation. New and important findings are continually being made of how the renin-angiotensin-aldosterone vasoconstrictor system regulates blood pressure. The kallikrein-kinin system and prostaglandins also are known to have a potent effect upon blood vessel dilation. The physiological effects of these hormones are also under investigation as is the role of nutrition, salt and weight control, and behavior.

The NHLBI Role

The NHLBI serves as the lead agency in the Federal hypertension education and control program. The Institute coordinates Federal and private sector efforts in hypertension including NHLBI research, clinical studies, clinical trials, demonstration and education programs, HSA (Health Services Administration) screening and care clinics, and other general activities of such agencies and HRA*, DOD*, NASA*, and others. Communication and coordination with public voluntary associations and societies is effected through the High Blood Pressure Education Coordinating Committee, chaired by the Director, NHLBI. Within the Federal sector, both research and education efforts are coordinated through the NHLBI Interagency Technical Committee, which coordinates overall Federal efforts focusing on cardiovascular diseases (including heart, blood vessel, lung and blood disorders, and blood resources).

Legislative History

When Congress mandated the creation of the National Heart Institute in 1948, research on hypertension was implicitly included in the statement of the Institute's primary mission, to:

> "conduct, assist, and foster researchers, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of heart diseases. . ." (PHS Act Section 412 (a), as established in 1948 by Public Law 80-655.)

In passing the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423), Congress greatly expanded the Institute's scope and mandates; and gave clear and firm support for hypertension research. The new law retained the broadly worded primary mandate, but expanded "heart diseases" to say "heart, blood vessel, lung, and blood diseases." More significantly, however, a new section was added to the Public Health Service Act, outlining a detailed and comprehensive National Program to explore the designated disease areas over a wide spectrum from basic research through clinical research, large-scale trials, and demonstration activities (Section 413, Public Health Service Act). Within this National Program, hypertension was specifically cited as an area for emphasis:

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*Health Resources Administration (HRA), Department of Defense (DOD), and National Aeronautics and Space Administration (NASA).

> "The Program shall give special emphasis to the continued development in the Institute of programs relating to atherosclerosis, hypertension, thrombosis, and congenital abnormalities of the blood vessels as causes of stroke . . ." (Underlining added, PHS Act Section 413(a).)

This statement, first written in 1972, has remained unchanged in the Institute's authorizing legislation through reauthorizations in 1975, 1977, and 1978, and is present in the current language.

In addition to giving emphasis to hypertension within the Institute's research program, Congress in 1972 cited hypertension for special attention for information dissemination activities. In the section of the Act establishing an Assistant Director for Health Information Programs and a mandate to provide such information to the public and health professionals is the following statement:

> "In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary diseases." (Underlining added, PHS Act Section 413(d) as established in 1972 by P.L. 92-423.)

Therefore, since 1972 the Institute's authorizing legislation has included specific statements mandating prevention, education, and control activities in hypertension, as well as research.

While the National High Blood Pressure Education Program and the Hypertension Detection and Follow-up Program are not specifically cited, but rather grew out of the above mandates, they have received Congressional attention in the legislative history of reauthorizations and appropriations. Tables 1 and 2 show the budget history of the hypertension programs, by mechanisms and major program emphasis, for FY 1978-82.

NHLBI

Table 1

NHLBI Hypertension Funds by Program Mechanisms, FY 1978-82

(Thousands of Dollars)

	1978	1979	1980	1981*	1982**
Research Grants					
Research Project Grants (R01 and P01)	$27,122	$33,965	$49,231	$37,649	$41,394
Research Centers	5,319	5,716	9,052	6,691	6,198
Other Research	2,168	2,104	2,517	1,976	1,659
Research Training	2,718	2,981	6,096	3,631	3,458
Research Contracts	21,226	17,985	15,560	8,757	8,092
Intramural Research	5,269	5,582	5,856	6,420	6,935
Other	5,115	5,467	6,283	6,113	6,335
TOTAL	$68,937	$73,800	$94,595	$71,237	$74,071

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*1981 Continuing Resolution
**1982 Revised President's Budget

Table 2

NHLBI Hypertension Funding by Major Program Emphasis, FY 1978-82

(Millions of Dollars)

	1978	1979	1980	1981*	1982*
Basic and Applied Research	$48.2	$54.9	$74.5	$55.8	$65.2
Clinical Trials*	13.2	8.2	7.5	6.3	1.9
National High Blood Pressure Education Program	7.6	10.7	12.6	9.1	7.0
TOTAL	$69.0	$73.3	$94.6	$71.2	$74.1

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*Data incomplete at this time (8/1/81).

Program Objectives and Activities

The NHLBI Hypertension Program encompasses the full spectrum of research: basic and clinical research to identify the causes and progression of hypertension; clinical trials to determine the effectiveness of treatment methods; and an education and information dissemination program to bring the results of research to bear on health problems as expeditiously and effectively as possible. Program management under the National Plan mandated by the National Heart, Blood Vessel, Lung, and Blood Act has been and continues to be guided by two primary goals:

- To improve understanding of the physiological and behavioral systems that control blood pressure, and the means by which these systems can initiate and/or exacerbate the development of hypertension, in order to significantly reduce the incidence of, and ultimately lead to the prevention of, hypertension.

- More effective therapy for those already afflicted, in order to reduce morbidity and mortality associated with hypertension and its sequelae.

An important element of the National Plan is the establishment of objectives for research. The following are the hypertension-related objectives for the next five years:

- To emphasize research on etiology and pathogenesis of hypertension,

- To encourage the development of improved methods and techniques for all aspects of hypertension research,

- To broaden the interdisciplinary base for contributions to hypertension research by attracting scientists to this field who traditionally have not been involved, or those unaware of the magnitude of their potential contributions if their efforts were directed toward this area of research,

- To evaluate the basic and clinical biomedical and biobehavioral research implications of the Hypertension Detection and Follow-up Program (HDFP) and implement appropriate actions to improve patient care, and

- To implement effective models of high blood pressure control on a community-wide basis.

Current program activity can be divided into three components: Basic and Clinical Research, Clinical Trials, and Education and Information dissemination.

Basic and Clinical Research

By far the largest single element of program activity relates to fundamental research on the causes and progression of hypertension. It is estimated that currently about 80 percent of NHLBI funds are devoted to hypertension research. Researchers are supported for both small and large research grants in a variety of university and clinical laboratory settings. A significant component of the NHLBI Hypertension Program is the network of research centers known as Specialized Centers of Research (SCOR): Hypertension. These centers encourage multidisciplinary research on hypertension topics over the entire research spectrum from basic to applied research.

The current research portfolio represents a response to research needs and includes studies initiated by investigators as well as areas for research suggested by the Institute. Table 3 illustrates hypertension initiatives by two methods of solicitation: Request for Applications (RFA) and Request for Proposals (RFP).

Clinical Trials

Clinical trials test the efficacy of preventive and treatment regimens and are the crucial step bridging the gap between research and practice. Hypertension-related trials are large-scale efforts requiring thousands of patients and tens of millions of dollars to complete. The results are critically important to therapy. Over the past five years NHLBI has supported two large-scale clinical trials related to hypertension.

The first, the Hypertension Detection and Follow-up Program, was recently concluded. The trial compared aggressive therapy for mild hypertension against simple referral care. The results from this $70 million trial showed that an aggressive treatment protocol (stepped-care) lowers mortality over five years from that of typical care (referred-care) by more than 17 percent. The result is of particular importance to the 25 million Americans with so-called borderline or mild hypertension who may benefit greatly from treatment. Indeed the impact could mean a reduction in annual health care costs of about $1 billion.

The second major trial related to hypertension is the Multiple Risk Factor Intervention Trial (MRFIT). This trial is testing the effectiveness of the simultaneous reduction of three risk factors: cholesterol, smoking, and blood pressure. This, the largest trial supported by NHLBI with over 13,000 subjects and a projected total cost of $130 million, is testing the effectiveness of risk factor reduction to determine whether and to what extent the reduction regimens are effective on both overall and cardiovascular mortality.

Education and Information Dissemination

The objective of this third major component of the hypertension program is to translate the results of research into practice and to the public. The

Table 3

Hypertension Initiatives, FY 1977-1981

(Number of Grants or Contracts, and Dollars Requested in Thousands)

Request for Applications		1977		1978		1979		1980		1981	
		No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
	High Blood Pressure in the Young	16	$2,681	15	$2,149	10	$1,623	6	$1,052	-	-
	Hypertension Education Grants	5	675	1	6	1	67	1	91	-	-
RFA-77-A	Evaluation Studies of Community HBP Control - Urban	2	416		-	2	507	2	554	2	$ 550
RFA-78G-G	Pilot Evaluation of HBP Control in Rural Community	-	-	-	-	3	705	3	708	3	747
RFA-78G-J	Role of Central Nervous System in Hypertension	-	-	-	-	12	906	12	907	10	783 est.
RFA-79G-G*	Hypertension SCOR	-	-	-	-	-	-	2	1,477	3	4,703
RFA-79G-F	Effects of Hypertension & Vasoactive Agents on Vasculature	-	-	-	-	10	1,036	7	612	10	879 est.
RFA-80G-A	Role of Microcirculation in Hypertension	-	-	-	-	-	-	9	721	9	747 est.

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*Dollars are competing $ only and do not include noncompeting funds.

Table 3 (Cont.)

Hypertension Initiatives, FY 1977-1981

(Number of Grants or Contracts, and Dollars Requested in Thousands)

Requests for Proposals		1977		1978		1979		1980		1981	
		No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
*RFP-77-17	Non-Human Primate Models of Atherosclerosis, Hypertension	2	$ 403	2	$ 457	2	$ 539	2	$1,239	-	-
RFP-77-18	Development of Prostaglandin & Kallikrein-Kinin Antagonists	5	379	5	353	3	227	-	-	-	-
RFP-77-19	Demonstration Programs Hypertension Control in Work Setting	-	-	3	640	3	520	3	540	-	-
RFP-77-20	High Blood Pressure Control Statewide	4	2,549	4	2,508	4	3,429	1	37	4	$3,923
RFP-77-29	Demonstration-Health Insurer's Role-Work Site High Blood Pressure Control	1	498	-	-	-	-	-	-	-	-
RFP-78-05	Development & Testing of Prostaglandin Antagonists	-	-	4	321	4	341	4	340	-	-
RFP-78-11	National High Blood Pressure Education Program	-	-	1	1,939	1	2,106	1	156	-	-
RFP-79-17	Demonstration of Impact of Statewide Coordination of HPB Control	-	-	-	-	3	1,355	3	3,983	-	-

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*New dollars only.

Table 3 (Cont.)

Hypertension Initiatives, FY 1977-1981

(Number of Grants or Contracts, and Dollars Requested in Thousands)

Requests for Proposals		1977		1978		1979		1980		1981	
		No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
*RFP-79-22	Health Hazard Appraisal in Industry	-	-	-	-	1	$ 150	1	$ 158	-	-
RFP-80-26	Non-Human Primate Models of Atherosclerosis & Hypertension	-	-	-	-	-	-	-	-	4	$2,299
	Dahl Hypertension-Sensitive and Resistant Rats	-	-	-	-	-	-	1	134	1	187
RFP-80-12	Estimation of Human Dietary Sodium Intake or Excretion	-	-	-	-	-	-	1	200	-	-
**RFP-80-15	Continued Surveillance of HDFP Population	-	-	-	-	-	-	14	2,073	1	1,644 est.
RFP-80-16	Continued Surveilance of HDFP Population Coordinating Center	-	-	-	-	-	-	1	0	-	-
RFP-80-07	National High Blood Pressure Education Program	-	-	-	-	-	-	1	2,196	1	1,851 est.

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*Evaluation dollars.
**New dollars only for FY 1980.
Note: Dollars for RFP 80-16 in FY 1981 are included with dollars for RFP-80-15.

Table 3 (Cont.)

Hypertension Initiatives, FY 1977-1981

(Number of Grants or Contracts, and Dollars Requested in Thousands)

Requests for Proposals	1977		1978		1979		1980		1981	
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
NHLBI-HSA Five-Site Demonstration of HBP Management	-	-	-	-	-	-	-	-	1	$ 250 est.
*Pilot Study of Survivorship & Causes of Death in U.S. Population	-	-	-	-	-	-	-	-	1	93 est.
Training										
Minority Hypertension Research Development Summer Program	7	$ 177	13	$ 333	15	$ 405	16	$ 583	16	550

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*Evaluation dollars.

hypertension education and information dissemination efforts are primarily, but not exclusively, through the National High Blood Pressure Education Program (NHBPEP). This program has been held chiefly responsible for the increases in knowledge and awareness of hypertension over the last decade. These changes, in turn, may be one of the primary contributing factors in the major decline in stroke deaths and overall cardiovascular mortality over the past decade. The NHBPEP has concentrated on marshaling the Nation's resources behind public and professional education to disseminate information on the full range of blood pressure issues. The information has ranged from the need for detection to a more recent program shift to an emphasis on patient compliance to therapy. The program includes an information collection and dissemination component, consultants to State programs, a media program, professional education components, and other subgroups.

Demonstration programs play a key role in the hypertension program. They are also a part of the NHLBI mandate for research on disease control and are a natural extension of the Institute's clinical trials and technology translation efforts. Currently six demonstration programs are under way:

- Statewide coordination of high blood pressure coordination and control activities. Seven states--California, Connecticut, Georgia, Maine, Maryland, Michigan, and South Carolina--are to coordinate their hypertension control programs by developing a coordinating council or alternative mechanism; by assessing the level of coordination before the contract, obtaining baseline data on prevalence, patient awareness and control status; by implementing a planned control program; and by preparing an inventory of resources. The NHLBI is monitoring these contracts to assure that minority populations are included at all levels.

- Pilot studies of high blood pressure control in two communities with a high prevalence of hypertension. These studies in local settings seek to identify acceptable models of high blood pressure control. The two communities, Detroit, Mich., and Berkeley, Calif., have large black populations.

- Pilot studies of high blood pressure control in rural communities with a high prevalence of hypertension. These studies are also designed to identify models of high blood pressure in two dispersed populations. Access to care and perceptions of the disease in rural populations are addressed. The projects are located in rural Georgia, North Carolina, and Kentucky. The Georgia and North Carolina projects are both directed to black populations.

- A grant to demonstrate the health and cost effectiveness of a hypertension control and education effort in rural central Mississippi using the private practitioner as a focus. This extensive research protocol addresses epidemiological, genetic, and environmental aspects of hypertension as well as designing and evaluating educational interventions. The population of this project is 50 percent black.

- Dietary interventions in three clinical settings which either reduce antihypertensive drugs required for control or increase maintenance of goal blood pressure. The three settings are Birmingham, Ala., Jackson, Miss., and the Bronx, N.Y. The Alabama and Mississippi projects address large black populations.

- Joint NHLBI-HSA grants to five community health centers for blood pressure control demonstrations. The Five Site Demonstration Program seeks to translate into medical practice the results of the Hypertension Detection and Follow-up Program for community health centers. The NHLBI, in cooperation with the Health Services Administration, launched this program to determine whether and how methods of stepped-care used in HDFP can be employed in a variety of community health settings. The program, recommended by the Black Health Providers Task Force, recently began.

Evidence of Program Performance

Several methods are used by NHLBI staff to monitor program performance. These methods include periodic advisory committee program reviews, focused evaluation studies, and the use of bibliographic and program performance statistics related to grant requests, approvals, and awards. The general NHLBI management strategy is outlined in the NHLBI Director's reports as well as in the Evaluation Plan. Briefly, the strategy integrates evaluation and planning in a yearly cycle of program reviews and needs assessment. The focus of the cycle is NHLBI decision-making relative to new program starts and the phaseout of existing programs. As noted previously, recommendations of the Hypertension Task Force will play a major role in the next several years with respect to new research opportunities.

The NHLBI evaluation projects supported under one percent set-aside funds are important to these information-gathering efforts. Briefly these projects include:

- Basic and Clinical Research

Hypertension: Research Base and Manpower

NHLBI 78-4	Evaluation of Progress in Hypertension and Pulmonary Research
NHLBI 78-6	Blood and Hypertension Research Manpower Data Base
NHLBI 81-308	Evaluability Assessment of the Minority Hypertension Research Summer Program

- Clinical Trials

NHLBI 81-307	Evaluation of the Hypertension Detection and Follow-up Program (Phase I: Evaluability Assessment)

NHLBI 82-302 Evaluation of the Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial

NHLBI 82-306 Evaluation of the Hypertension Detection and Follow-up Program (Phase II: Physician Practice)

- Education and Information Dissemination

Hypertension: Knowledge and Awareness

NHLBI 77-3 Evaluation of Patient Tracking Systems

NHLBI 78-1 Survey on Hypertension Awareness Knowledge and Behavior

NHLBI 79-302 Evaluation of Health Hazard Appraisal in Work Setting Preventive Medicine Programs

NHLBI 80-304 Evaluation of Statewide Hypertension Programs

NHLBI 80-305 Evaluation of Compliance Improvement Program

NHLBI 82-303 Public Knowledge Attitudes and Behavior Regarding High Blood Pressure: An Interim Assessment

Hypertension: Media Related

NHLBI 77-5 Health Message Testing

NHLBI 80-306 Evaluation of the Effect of High Blood Pressure Media Messages on Physicians

NHLBI 80-310 Assessment of Audience Exposure to Television Public Service Messages on High Blood Pressure

Hypertension: Community Demonstrations

NHLBI 81-314 Evaluation of a Demonstration Program for Hypertension Control Using Community Health Centers

NHLBI 82-308 Evaluation of a Demonstration Program for Hypertension Control Using Community Health Centers (Phase II: Conduct of the Evaluation)

(Short descriptions of these studies are included as an attachment to this section.)

The following section addresses program progress for the research program (which includes basic and clinical research and clinical trials) and the education information dissemination program. The year 1972 is used as the point of reference.

Research Program Performance

Two broad goals, one short-range and the other long-range, were set by the Institute in 1972 to guide its research efforts:

- Short-range goal: to increase understanding of the underlying dysfunction in essential hypertension and optimize the use of currently effective treatments for hypertension.

- Long-range goal: to prevent hypertension.

The actions taken to implement these goals can be grouped into four major categories: studies related to the etiology of hypertension; clinical trials to investigate the effects of therapeutic intervention; epidemiologic studies; and the development of animal models.

The State of the Science, 1972. By 1972, drug therapy for controlling hypertension in severe and moderately severe cases was available and effective. It had already been shown that the risks of stroke, heart failure, and kidney failure could be significantly reduced in patients who received adequate antihypertensive drug therapy. The therapy, however, involved lifelong adherence to a drug regimen which often had unpleasant side effects. It was thus clear to the scientific community in 1972, as now, that a matter of high priority would be to find the cause or causes of hypertension in order to prevent its development. At that time, the etiology of hypertension was not known nor was its pathophysiology clear, although many leads were available.

Hypertension was thought to be a condition resulting from a breakdown in the complex control system that maintains equilibrium between the constricting and dilating forces of the arterial walls. The regulation of normal blood pressure was pictured as dependent upon a balance of hemodynamics, humoral, and many other factors operating at one time.

It had been known for 150 years that the kidney was implicated in hypertension. There was considerable evidence by 1972 to indicate that the kidney had a blood pressure elevating function and possibly a blood pressure lowering function. Renin and angiotensin were two substances linked to the elevation of blood pressure.

The adrenal cortex was also believed to have some relationship to hypertension because drugs which antagonized the action of the mineralocorticoid hormone aldosterone had proved useful in the treatment of some forms of hypertension. Similarly, the autonomic nervous system was suspected of being important, since manipulation of this system with blocking agents and drugs had proved effective in lowering elevated blood pressure. Salt intake was also believed to play a role in the genesis of hypertension, but the nature of the relationship needed further clarification.

Prior to 1972, a suitable animal model of human essential hypertension was not widely available, which limited research on the etiology and pathophysiology of hypertension, especially the biochemical and genetic aspects of the problem. Clinical trials and demonstration programs were also needed to determine the benefits of drug therapy. Recognizing that a balanced research effort, including all aspects of the problem, was required, the Institute moved forward to intensify its hypertension research program.

Progress Related to the Etiology of Hypertension

Considerably more is known now than in 1972 about the vasodilator and vasoconstrictor systems and their relation to hypertension. Biochemical studies over the past five years have added important new information to our understanding of the pathogenesis of hypertension. Studies on blocking agents have shown that irregularities in the renin-angiotensin system are related to hypertension in some patients; studies have linked the excretion of low amounts of kallikrein to elevated blood pressures; and prostaglandin studies suggest that defects in prostaglandin metabolism may have a genetic component that predisposes test animals to hypertension.

While evidence exists that renin levels are an important factor in most essential hypertension, some hypertensive patients do not show elevated renin levels. In these cases, it is possible that mineralocorticoid activity may be critical. Increased levels have been detected in the urine of spontaneously hypertensive rats. The search continues for new mineralocorticoids in low renin, essential hypertension patients.

All of these findings have added considerably to our understanding of the biochemical events that affect the etiology and pathogenesis of hypertension. Yet more information is needed, and further research in this area is required. Consequently, the Institute is continuing to fund basic research on all aspects of hypertension, including the support of studies on the renin-angiotensin-aldosterone vasoconstrictor system and on the vasodilator system of kallikrein-kinins and prostaglandins.

Progress in Clinical Trials

Clinical trials are a key activity, bridging the gap between basic and clinical research and medical practice. They provide the definitive test of preventive or therapeutic regimens. Several clinical trials have concluded or are in progress, the main goal being to evaluate the effectiveness of intensive antihypertensive therapy.

The Hypertension Detection and Follow-Up Program (HDFP). By 1972 published data from the Veterans Administration Cooperative Study of Hypertension demonstrated that reduction in morbidity and mortality could be attained by treating men with fixed diastolic blood pressure over 105 mm Hg. Similar trends occurred for those with fixed diastolic blood pressure between 90-104 mm Hg. Results and current trends from other studies supported these findings. However, prior to inception in 1972 of the Hypertension Detection and Follow-up Program, it was not known whether antihypertensive therapy applied to all hypertensives in the general population and whether making use of existing medical knowledge could significantly reduce morbidity and mortality from hypertension in communities. Moreover, in blacks, despite their high prevalence of hypertension, it was not known whether treatment would be effective. In addition, the question of treatment effectiveness also remained for the relatively young patient, for women, and for the millions of Americans with mild hypertension.

The primary hypothesis tested by this clinical trial was that intensive blood pressure control under stepped-care for five years can significantly reduce mortality compared to that under referred care. Stepped-care is that method of treatment in HDFP clinics in which a diuretic is given initially and additional antihypertensive agents are added in a time-structured stepwise fashion until goal blood pressure is achieved. Referred-care represents referral to private physicians and other community sources of care. Participating in this study were 10,940 patients studied in 14 clinical centers, a coordinating center, EKG center, central laboratory, and monitoring laboratory. Dramatically, HDFP showed that systematic effective management of hypertension has great potential for reducing mortality for the large numbers of people in the U.S. population with high blood pressure, including those with "mild" hypertension. Blood pressure control was consistently better for the stepped-care group than for the referred-care group.

Five-year mortality from all causes was 17 percent lower for the stepped-care group compared to the referred-care group and 20 percent lower for the stepped-care subgroup with entry diastolic blood pressure of 90 to 104 mm Hg (so-called mild hypertension) compared to the corresponding referred-care subgroup. For white men, black men, and black women deaths from all causes were substantially lower--by 15 to 28 percent--for the stepped-care subgroup compared to the referred-care subgroup. These results, which show a clear advantage for systematic care, become especially significant when one considers the improved routine care of high blood presssure that has been provided in American communities in recent years.

The Multiple Risk Factor Intervention Trial (MRFIT). Hypertension is one of the major risk factors for heart attacks currently being studied in the Multiple Risk Factor Intervention Trial (MRFIT). Data from this study will help to determine whether a significant reduction in heart attacks can be achieved by the reduction of the combined risk factors of high blood pressure, high blood cholesterol, and cigarette smoking in men at risk of coronary heart disease. The study is following over 12,800 subjects in 20 clinics nationwide for six years.

Systolic Hypertension in the Elderly (SHEP). Now in its planning phase, this clinical trial will test the efficacy of stroke prevention in the elderly. Standard hypertension drug therapy will be used in 500 patients in five clinics in a pilot study performed in cooperation with the National Institute on Aging.

Epidemiological Studies

Long-term epidemiological studies have also been initiated in an effort to identify persons at risk of developing hypertension. The Epidemiology of Hypertension in the Young Program is attempting to identify the precursors and correlates of elevated blood pressure in all age groups. This program's main areas of emphasis are genetic and familial studies; "tracking" studies in which blood pressure in children is recorded periodically over time; follow-up studies on factors measured in prenatal and infant studies; studies in children whose mothers had toxemia of pregnancy; and studies of dietary, psychological, growth, and other factors which may relate to elevated blood pressures in the young.

Data are now available from the Framingham Study, a prospective study of 5,209 individuals in Framingham, Mass., which in 1977 completed 29 years of followup. The study has revealed that hypertension, in addition to its role as a risk factor for heart attack, sudden death, and stroke, is the major etiologic precursor of congestive heart failure. One important aspect of this analysis is that it indicates that elevated systolic pressure plays a role equal in importance to elevated diastolic pressure in the development of congestive heart failure. This finding is worthy of further investigation since diastolic pressure had traditionally been considered the more critical of the two blood pressure readings.

Animal Models

In an effort to develop animal models for hypertension, critical for research progress, the NIH Division of Research Services has arranged to introduce three strains of hypertensive rats into its facilities. These strains, the New Zealand, Milan, and Dahl S and R rats, will be bred in colonies and eventually made available to all investigators. NHLBI played a major role in encouraging the establishment of resource colonies of these and other strains. Attempts are also in progress to develop nonhuman primate models of essential hypertension.

Hypertension Task Force

The Task Force on Hypertension was established to assess the current state of hypertension research. The Task Force, whose work was concluded in 1979, consisted of 20 members, most of whom chaired 12 scientific subgroups. Each subgroup produced a summary report, an evaluation of the current state of knowledge, and recommendations for future research emphasis, manpower and training needs, animal models, resources, and new technology. Among the major topics covered by the Task Force report are the following:

- Local and systemic hemodynamics
- Neural control of the circulation
- Vascular smooth muscle: nerve terminals

- Hypertensive vascular disease
- Vascular smooth muscle: contractile apparatus
- Pediatrics
- Genetics
- Prostaglandins
- Kallikrein-kinins
- Renin-angiotensin-aldosterone
- Salt and water
- Therapy
- Pregnancy
- Obesity

In each of these areas, the Task Force recommended study of specific aspects of the problem that are amenable to research and are central to improving prevention, treatment, and control approaches.

In addition, the Task Force recommended education and training, development of animal models, and specific forms of research resources such as standard reagents or central pools of chemical and pharmacologic tools. These recommendations, based on an analysis of scientific knowledge and an evaluation of progress, will guide the Institute in its future efforts.

Progress in Health Education

The NHLBI focus on hypertension-related health education is the National High Blood Pressure Education Program (NHBPEP). Since its inception in 1972, the initiatives of the program have included the cooperative development and dissemination of treatment recommendations, overcoming barriers to cooperation among health professionals, improving dietary management of high blood pressure, improving interaction between patients and health professionals, and assisting in developing better high blood pressure control in rural communities and in work settings. In addition, the program maintains a core of activities including an information center, technical assistance at the State and local levels, and materials development.

Allied with NHBPEP, the NHLBI has also initiated demonstration programs in statewide control, control in rural communities, and control in work settings, which will provide additional resources and understanding about effective approaches to high blood pressure control.

Progress in specific dimensions of the hypertension health education program is evident at various levels. For example:

- A survey performed in 1973 to assess public knowledge about high blood pressure and help plan educational activities for the NHBPEP was repeated in 1979. The findings show clear and striking changes in the public's understanding of hypertension. In 1979, 73 percent of the public, compared with 63 percent in 1973, believed hypertension is a serious condition. Between 1973 and 1979, the segment of the public having their blood pressure measured within the prior year increased from 73 to 83 percent. Other surveys show similar gains. (Figures 1 and 2.) Other results indicate that nearly twice as many people now know what a normal blood pressure is, and 40 percent more people now understand that hypertension does not have reliable symptoms. In addition, more people believe effective treatment is available for hypertension; likewise, greater numbers of patients are following their prescribed therapy.

- From 1972 through 1979, age-adjusted death rates from hypertension-related cardiovascular diseases declined by 35 percent, while the decline for cardiovascular diseases not related to hypertension declined only 12 percent. (Figure 3.) In addition, preliminary data analysis indicates that stroke death rates, which have declined precipitously in the United States since the NHBPEP began, are measurably lower over time in communities that have active education programs compared with those that do not.

- A 1977 survey indicates that physicians' practices generally concur with national treatment recommendations in areas of screening, detection, and management.

- The Program has developed consensus statements on critical hypertension control issues including definition of hypertension and treatment regimens.

- As a direct response to recommendations from the Black Health Providers Task Force (BHPTF), NHLBI, in cooperation with the Health Services Administration, is undertaking the Five Sites Program. The demonstration projects will both implement selected recommendations from the BHPTF in community health centers and apply methods and lessons learned from HDFP in these centers. Basic planning for the program has been completed. Five community health centers will be involved, all heavily minority, one representing at least a forty percent Hispanic population, and two rural centers with populations at least 70 percent black.

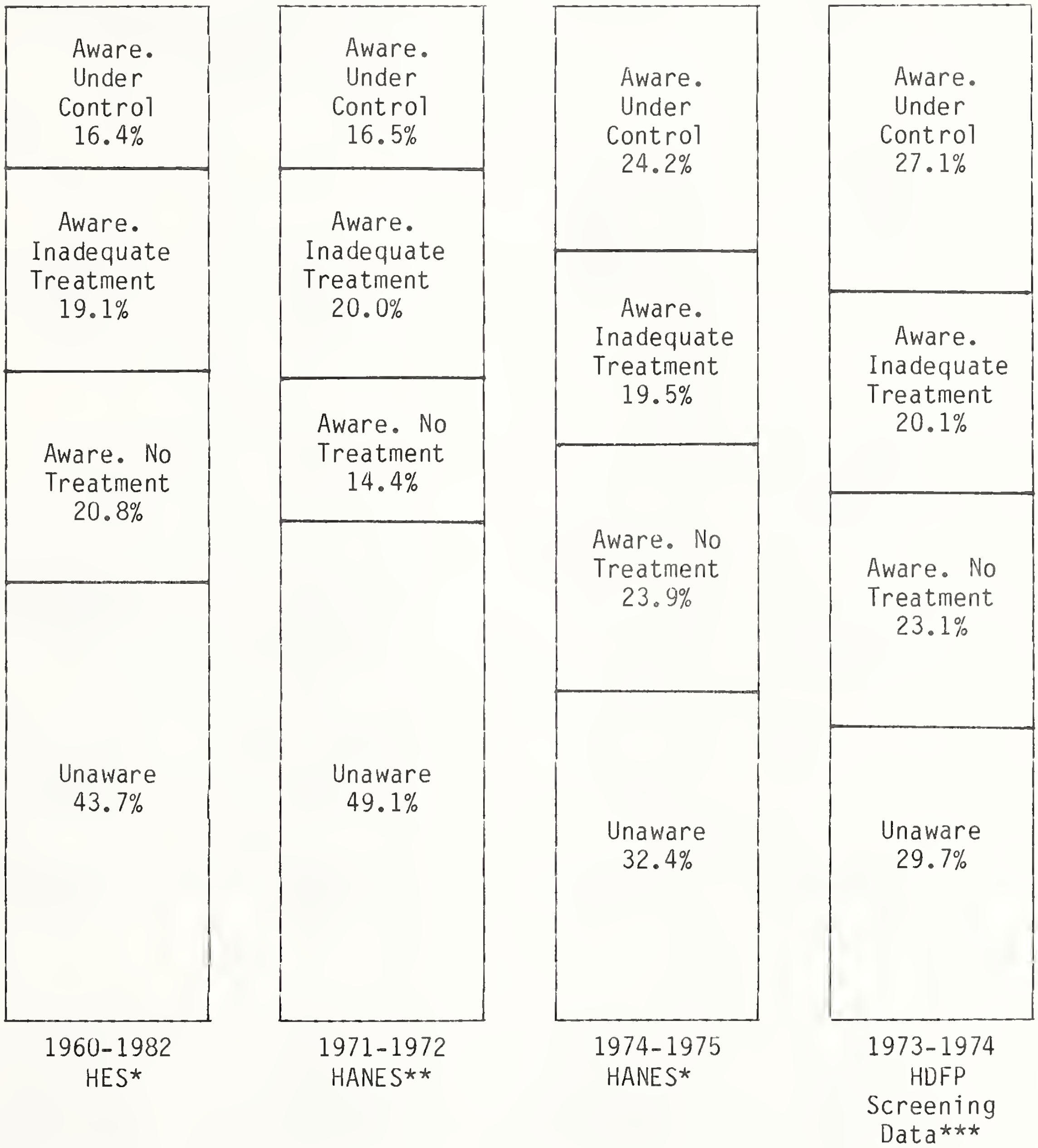
Interagency Coordination

NHLBI is the lead agency in the Federal hypertension program. Coordination is effected through the legislatively mandated Interagency Technical Coordinating Committee and the Hypertension Education Coordinating Committee, the latter focusing primarily on issues related to hypertension education. Specific areas of cooperation and coordination are many, including coopera-

Figure 1

PERCENT OF HYPERTENSIVES IN SPECIFIED AWARENESS, TREATMENT, AND CONTROL STATUS CATEGORIES

Hypertension has been defined as ≥ 160/95 mm Hg or those taking medicine for high blood pressure.



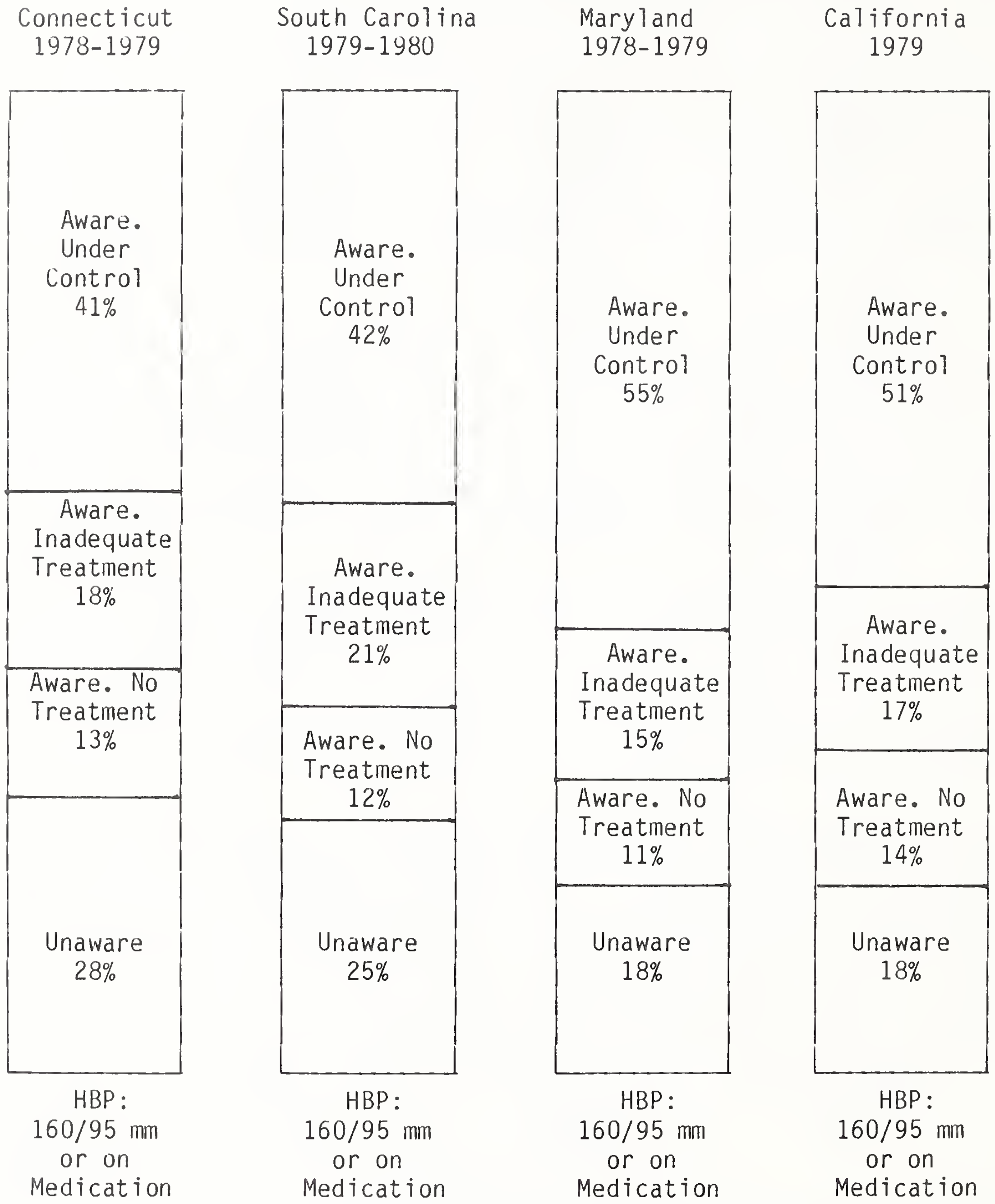
*Blood pressures based on the average of the three measurements and a population aged 25-74.

**Blood pressures based on a single measurement and a population aged 18-74.

***Blood pressures based on a single measurement and a population aged 30-69.

Figure 2

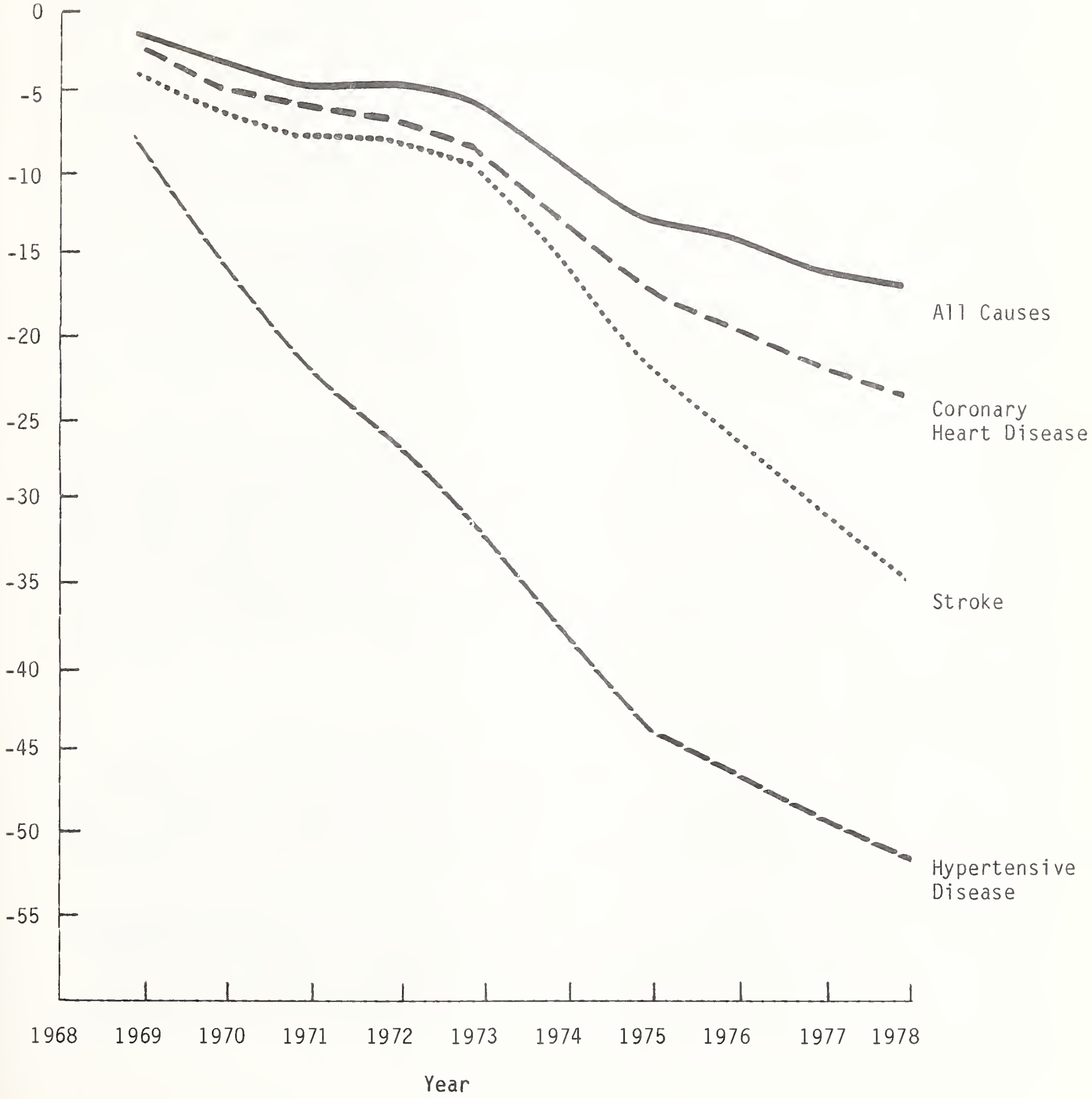
PERCENT OF HYPERTENSIVES IN SPECIFIED AWARENESS, TREATMENT, AND CONTROL STATUS CATEGORIES, PRELIMINARY DATA FROM FOUR STATEWIDE DEMONSTRATION PROJECTS



NHLBI

Figure 3

PERCENT CHANGE SINCE 1968, FOR ALL CAUSES OF DEATH, HYPERTENSIVE DISEASE, CORONARY HEART DISEASE, AND STROKE



tion with the VA on clinical studies and trials, Bureau of Community Health Services (BCHS) of HSA on a revenue-sharing formula and distribution of program materials, FDA-NHLBI coordination of a physician survey, joint planning with HSA on a demonstration of HDFP treatment applied in HSA community hypertension treatment clinics.

Studies Prepared to Assess Program Performance

As NHLBI nears its tenth anniversary of the National Heart, Blood Vessel, Lung, and Blood Disease Program, the Institute is performing a comprehensive assessment of progress since 1972 across all its program areas, including hypertension. The review effort is now under way. Evaluation projects under the one percent set aside program have been listed in an earlier section.

Problems Cited and Responses by the Administration, Congress, or Other Organizations

No significant problems have been cited. Congressional interest and the NHLBI response to that interest on several issues are cited below.

Demonstration of Hypertension Control

The House Appropriations Report for FY 1977 directed NHLBI to conduct pilot demonstrations of hypertension control in four to six States to test the effects of statewide coordination. In response, during FY 1977 four States (California, Connecticut, Maryland, and South Carolina) were awarded contracts for this purpose. Three additional awards (Georgia, Maine, and Michigan) were made in FY 1978. These contracts are proceeding well and according to plan. Outcome analyses from the first four contracts are expected in FY 1982-1983.

Hypertension Among the Elderly

Questions with respect to hypertension among the elderly were raised in a hearing before the Subcommittee on Health and Long-term Care of the Select Committee on Aging, July 21, 1977 (H.R. Committee Publication 95-102). During the hearing Congressman Claude Pepper noted that "our goal . . . is to examine the adequacy of Government efforts to address this problem." NHLBI assisted Committee staff in acquiring data for preparation of the report. In addition, NHLBI testified before the Committee that, in a related activity, the Institute developed and promulgated consensus-based guidelines on detecting and treating hypertension in the elderly. As noted in this report under the discussion of clinical trials, NHLBI and NIA have initiated planning and pilot studies for a clinical trial to examine benefits of treating isolated systolic hypertension in the elderly.

Cooperation Between NHLBI and HSA

In Senate Appropriations Report No. 94-997, June 26, 1977, two points are raised concerning cooperation between HSA and NHLBI in fighting hypertension:

Page 45: "In addition, the Committee directs the Institute to work very closely with the Health Services Administration in locating and treating hypertensive victims." Senate Appropriations Committee Hearings for DHEW 1978, Part 2.

Page 1245 - Question: Does your (NHLBI) hypertension program overlap with the one in Health Services (HSA)?

In fact, the NHLBI effort emphasizes coordination of research and education aimed at increasing hypertension control. The HSA effort supports limited hypertension control (care provision) by State health departments and their grantees or contractors. Coordination of these efforts is achieved by periodic staff interaction between both agencies, mutual review and exchange of educational and policy guidance materials, and joint sponsorship of selected demonstration projects.

Black Health Providers Task Force

In the Labor, Health and Welfare Appropriations Hearings for 1980 (H.R. Appropriations Committee, 96th Congress, first session, part 4, National Institutes of Health) Congressman Louis Stokes raised the question (page 735): "Are you committed to fully funding the work until it is completed?" NHLBI has supported the development of the report by the Black Health Providers Task Force. The Institute published and disseminated that report and has detailed the Institute response to its 85 recommendations among both government and private sector organizations. In addition, NHLBI has committed its support, jointly with the Bureau of Community Health Services, HSA, for a 5 year, 5-site services delivery research effort.

Major Barriers and Issues Relating to Performance

Agency barriers or constraints are divided into four categories: those dealing with the Basic Research Program; those related to the Health Education Program; budgetary constraints; and fundamental constraints that derive from a general resistance to behavioral change.

Basic Research Program

A lack of sufficient numbers of high caliber research scientists with training in the behavioral research sciences is constraining research on the behavioral aspects of hypertension etiology, pathophysiology, and treatment.

Health Education Program

Limitations in the available data do not allow adequate assessment of program needs and therefore constrain planning. Specifically:

- Death rate data are relatively complete but apportionment of deaths as related to hypertension is difficult.
- Some data on public knowledge related to hypertension effects, treatments, and causes is available but generally are not associated with blood pressure measurements in individuals.
- Infrequently gathered prevalence data on hypertension limit the analysis of change.

Budgetary Constraints

Despite progress, personnel ceilings limit adequate response to the NHLBI Congressional mandate, resulting in outside contracting to carry out activities rather than development of a career cadre. Program expansion, particularly for demonstration efforts, is limited.

Resistance to Change

The long time required for individual behavioral change and societal institutional change requires that planning be realistic with limited, reachable goals.

- Health system change is a slow process: new procedures and organizational relationships are adopted slowly and at an uneven pace across the Nation.
- National and community organizational motivation tends to wane with the long time required to effect change.

Evaluation Projects Related to the NHLBI Hypertension Program

Hypertension: Research Base and Manpower

NHLBI 78-4 Evaluation of Progress in Hypertension and Pulmonary Research. This completed project tested the use of bibliographic and citation analysis in determining whether research progress can be measured quantitatively using these techniques in a narrowly defined research area. The project has shown that these techniques can provide critical, quantitative data on research progress, and enable the Institute to better relate its actions to eventual program outcomes. Such measures would be important adjuncts to the advisory committees and working groups currently employed by the Institute as a primary measure of research area change. The Institute expects these methods to be used on the update of the National program plan.

NHLBI 78-6 Blood and Hypertension Research Manpower Data Base. This project is developing a data base to enable the Institute to (1) estimate and track the pool of researchers now included in blood and hypertension research, (2) assist in the assessment of past training programs, and (3) develop future projections for research training. The project has periodically queried investigators involved in the research areas as to their activities and interests. A final report is now being prepared and the information system is being turned over to the Institute.

NHLBI 81-308 Evaluability Assessment of the Minority Hypertension Research Summer Program. This project will address the feasibility of, and plan for, evaluating the Minority Hypertension Research Summer Program. This program encourages minority biomedical students and faculty toward biomedical research careers through a focus on hypertension research. The program is now in its fourth year and has progressed to the point that an evaluability assessment is appropriate. Activities under the project will include: the identification of the objectives of the Institute, the minority institutions and the research centers included in the program; and identification of measures for evaluating progress toward these objectives. Of particular importance will be the evaluation planning to relate short-term objectives reflective of program performance to the long-term objectives related to research careers. An RFP is under preparation.

Hypertension: Knowledge and Awareness

NHLBI 77-3 Evaluation of Patient Tracking Systems. This completed project assessed experience to date on hypertension treatment compliance (patient tracking) systems. The results of an inventory of systems, which identified and characterized systems nationwide, has shown that no system has been demonstrated to be effective but that several seem to have potential. The results from the study identified the need for Institute involvement in this area and led to the development of a guide for such activities.

NHLBI 78-1 Survey on Hypertension Awareness Knowledge and Behavior. This activity, completed in April 1980, is a six-year follow-up survey on public knowledge and behavior with respect to high blood pressure (NHLBI 78-1).

This survey provides a major benchmark for the Institute in its efforts to determine the effectiveness and needs with respect to high blood pressure education. The report is now being printed and has already proven useful to the Institute in its high blood pressure programming.

NHLBI 79-302 Evaluation of Health Hazard Appraisal in Work Setting Preventive Medicine Programs. As part of its research program, NHLBI is determining ways to effectively implement risk factor reductions. Part of this effort is concerned with programs at the workplace. This project seeks to evaluate the potential of health hazard appraisal to serve as a vehicle for establishing and conducting effective hypertension and other risk factor control programs at the workplace and to establish data collection procedures and analysis to be used to evaluate the workplace efforts in health hazard appraisal. This project is currently underway and making satisfactory progress.

NHLBI 80-304 Evaluation of Statewide Hypertension Programs. This project will perform an interim evaluation and develop a final evaluation plan for the 5-year NHLBI efforts in statewide control of hypertension. Several contracts with State agencies in Connecticut, California, Georgia, Maine, Maryland, Michigan, and South Carolina are designed to encourage and coordinate efforts to combat high blood pressure. The project is under way and a draft evaluation plan has been prepared.

NHLBI 80-305 Evaluation of Compliance Improvement Program. A weak link in the chain of hypertensive control is the failure of patients to follow through on the health provider's recommendations for treatment. Recognizing this problem, the Institute sponsored a grant program to develop a better understanding of, and improve methods for, achieving compliance. The purpose of this project is to evaluate the results of the grants supported under the program, to integrate these findings with other recent work on compliance, and to formulate recommendations on future research for the Institute. In addition, the project is developing recommendations for the National High Blood Pressure Education Program on actions to improve patient compliance.

NHLBI 82-303 Public Knowledge Attitudes and Behavior Regarding High Blood Pressure: An Interim Assessment. This project is designed to gather ongoing national trend data on public knowledge, attitudes, and behavior for a limited number of areas in the National High Blood Pressure Education Program. In addition to a random sample of individuals across the United States the survey will also include focused group interviews with hypertensives and family members to provide additional detail. The project will be implemented as additional questions to a routine survey conducted by one of the national polling organizations.

Hypertension: Media Related

NHLBI 77-5 Health Message Testing. Cosponsored by the National Cancer Institute and the Office of the Secretary, HEW, this project is developing a system for presenting health education messages before these messages are made final and distributed to the media. The first stage of this project

(NHLBI/NCI 77-5) developed and tested TV messages. This project continues the testing of the system and expands it to include print testing as well as the electronic media. The project is in its final year.

NHLBI 80-306 Evaluation of the Effect of High Blood Pressure Media Messages on Physicians. This project will assess the impact on physicians of popular media messages aimed primarily at patients. Health education and promotion programs reach both patients and physicians, yet their effect on physicians is not known. This project will address whether health professionals are influenced or reinforced by information in the general mass media, including public service announcements on radio or TV and messages in local newspapers. A contractor has been engaged and the project is under way.

NHLBI 80-310 Assessment of Audience Exposure to Television Public Service Messages on High Blood Pressure. Perhaps the major NHLBI effort directly related to prevention, education, and control is the National High Blood Pressure Education Program. This program utilizes a variety of mechanisms to increase public and professional awareness of the dangers of hypertension and ways of treating the problem. The electronic media are used extensively in the program. In order to determine the effectiveness of the media on a nationwide basis, it is necessary for the program to know the extent to which these messages are aired. This project will monitor on a periodic basis the airing of messages across the country. The NHBPEP program has a high investment in such messages, which must be used to be effective. If the messages are not being used or are used during non-prime time, the program will be able to respond, for example, by changes in message style, or by direct discussions with program managers. Procurement difficulties have postponed implementation of the project, but resolution is expected by April 30.

Hypertension: Community Demonstrations

NHLBI 81-314 Evaluation of a Demonstration Program for Hypertension Control Using Community Health Centers. One of several steps in the dissemination of the results of the recently completed NHLBI clinical trial, the Hypertension Detection and Follow-up Program (HDFP), is a demonstration of a hypertension control program in a community health center setting. This evaluation project is the first phase of a three-phase project to evaluate the demonstration program. The project will involve the design of a format for the conduct of the demonstration, the design of an evaluation methodology, the selection of sites, and the collection of necessary baseline data. The implementation and evaluation of the demonstration will be performed in subsequent phases over a five-year period. The results of the evaluation are expected to identify how much of the clinical trial protocol can be implemented in an existing health care system, and whether the approach is economically feasible. The design phase is now under way, using a panel of consultants and in-house staff.

NHLBI 82-308 Evaluation of a Demonstration Program for Hypertension Control Using Community Health Centers (Phase II: Conduct of the Evaluation). Phase I of this project (submitted as NHLBI 81-314) is now developing an evaluation strategy to assess the impact and effectiveness of the application of methods used in the Hypertension Detection and Follow-up Program in community health care centers serving minority populations. The development of the evaluation methodology is currently under way, as is the selection of sites and a determination of the necessary baseline data. Beginning in FY 82 the evaluation itself will be undertaken. Changes in the funding of these community health care centers (now anticipated to be funded through block grants) may necessitate a change in evaluation strategy. In any case this project will carry out evaluation as specified by the working group convened under the current project.

Hypertension: Clinical Trials

NHLBI 81-307 Evaluation of the Hypertension Detection and Follow-Up Program. The Hypertension Detection and Follow-up Program (HDFP), one of the Institute's large scale clinical trials, concluded in January 1980. This $70 million program has shown the effectiveness of treating relatively mild hypertension. This project will continue and expand the Institute's efforts to track the impact of this trial. The project will focus on Institute and other efforts to disseminate results of the trial, on changes in health practice, and changes in public knowledge. A conference will be held in June to assess and discuss the implications of this trial for patients, physicians, and the public at large.

NHLBI 82-302 Evaluation of the Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial. These large-scale clinical trials are scheduled to terminate in 1983 and 1982 respectively. The Coronary Primary Prevention Trial is determining whether cholesterol reduction by drug therapy will significantly lower coronary heart disease rate in a group of hypercholesterolemic but otherwise healthy men; the Multiple Risk Factor Intervention Trial (MRFIT) is assessing whether a special intervention program to simultaneously lower serum cholesterol, reduce blood pressure, and eliminate cigarette smoking will result in a significant reduction in mortality from coronary heart disease. In essence the CPPT is testing the so-called lipid hypothesis; MRFIT is testing the effectiveness of lowering several risk factors simultaneously. This evaluation project will assist the Institute in two ways: first, it will help the Institute determine whether and in which ways the clinical trials have affected practice, and secondly, it will assist the Institute in disseminating the results of the trial for maximum effectiveness. The project will survey current physician practice toward treating patients with elevated risk factors, the survey to take place before the results of the clinical trials are released. Subsequently, another survey will be performed after the results of the clinical trial have been released to determine clinical practice. The results from the first survey will be used by the Institute in designing the dissemination program for the clinical trials.

NHLBI 82-306 Evaluation of the Hypertension Detection and Follow-up Program (Phase II: Physician Practice). This project will continue evaluation project NHLBI 81-307, Evaluation of the Hypertension Detection and Follow-up Program. The latter project is a broad-based effort to determine the impact of the trial. The project proposed here will focus on the change in physician practice related to hypertension detection and treatment. A previous study was performed under joint FDA/NHLBI sponsorship in 1978. The Hypertension Detection and Follow-up Program (HDFP) has recently extended validated therapy for high blood pressure to the mild and moderate blood pressure ranges. There is a growing feeling, however, that the stepped-care approach to therapy, which attempts to use non-pharmacologic means to control blood pressure before drugs are used, may not be widely adopted. The survey to be conducted under this project and the previous survey will provide important data to the National High Blood Pressure Education Program and to the investigators of the HDFP on current practice and will therefore provide information on appropriate directions for information dissemination. (Because of the need to make this survey and the previous survey compatible, it is not anticipated that this project will be a direct component of NHLBI 82-302 above; however, it is expected that the projects will be coordinated.)

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Director's Overview

Significance of Health Problems

Nowhere is the burden of illness greater or the quality of life more significantly marred than in the chronic debilitating disorders of the nervous system. Current estimates indicate that more than 50 million persons in the United States are affected with 500 or more neurological and communicative disorders and that the resultant health care costs exceed $65 billion. People of all ages are stricken by these disorders, from the congenital anomalies, genetic diseases, and infections of early life (such as spina bifida, cerebral palsy, Tay-Sachs disease, muscular dystrophy, and meningitis), through the disorders of youth and early adult life (such as epilepsy, myasthenia gravis, head and spinal cord injuries, multiple sclerosis, and Huntington's disease), to the afflictions of adult life and the elderly (such as stroke, Parkinson's disease, amyotrophic lateral sclerosis, brain tumors, and the dementias, including Alzheimer's disease). Across this spectrum must be placed the disorders of communication, hearing, speech, and language, such as congenital deafness in the child, deafness acquired from infections or ototoxic drugs at any age, and the presbycusis or the dimming of hearing acuity in the older adult; the language-impaired child and the aphasic adult; and impairment of speech, including cancer of the vocal cords and larynx.

Research Strategy

The magnitude of societal costs due to mortality and long-term suffering places high priority upon basic research and constitutes one of the greatest challenges confronting the neuroscience research community in our attempts to improve the quality of life. Since the fundamental biochemical and pathophysiological processes underlying most of these disorders of the nervous system are only beginning to be understood, continued emphasis on basic and clinical research is needed. Frequently, preventive interventions do not yet exist, diagnostic procedures are often nonspecific, and treatment is either nonexistent or only partially effective. To meet these existing challenges, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has adopted, by policy, the strategy of giving priority to the utilization of its available resources for (1) improving the Institute's research training endeavor, with special emphasis on clinical research training and career development; (2) safeguarding and enhancing its intramural research program; and (3) stabilizing the support of individual research project grants.

Based on manpower studies and reports from professional and voluntary societies, the Institute recognizes that there is a serious shortage of clinical investigators in the neurological and communicative disorders as a result of significant reduction in research training funds since 1976. Therefore, NINCDS plans additional new and competing national research service awards with emphasis on clinical research utilizing the methodologies of neuroimmunology, neurovirology, and neuroendocrinology. In addition, special emphasis will be given to the problems of hearing loss, speech and language pathology, and spinal cord injury. Although stability of research grant support will tend to give some assurance of stable support for a career in clinical research, the Institute will reinforce this through increases in its program of Teacher Investigator Awards (TIA) designed specifically to develop, establish, and encourage young clinical investigators. The intramural research program will receive additional funds for "Other Objects" and for positions to compensate for decreases in the past and to provide for the establishment of its cerebral metabolic studies utilizing PETT (positron emission transverse tomography) and for clinical research facilities in otolaryngology, medical neurology, surgical neurology, and neuroimmunology.

The Institute has established as a goal the stabilization of support of competing research projects at half the amount allocated for noncompeting projects, so that competing projects will receive one-third of the total research grant funds.

By way of illustrating the results of the unprecedented explosion of new knowledge about the basic functioning of the brain and nervous system, a few research leads may be mentioned. In the area of central nervous system (CNS) regeneration, the effectiveness of Naloxone and corticosteroids in the treatment of acute spinal cord injury is being tested; the physiopathology, endocrinology, and biochemistry of the intact and traumatized nerve tissue are being intensively studied as to plasticity, reversibility, and the capacity to be restored to normal; several nerve growth factors have been recently identified, and research on traumatized and transected spinal cords show in some higher animals the potential for regeneration. All these leads and others point out specifically the possibility of developing needed information by more research on neural regeneration. Similarly, initiatives are under way in neurotoxicology to determine which drugs are toxic to the nervous system, to study the effect of heavy metal environmental (air, water, food) exposure on the brain function, such as hazards in the home, office, and industrial setting, as people use gasoline, house paints, artificial food coloring dyes, etc., and in the process are exposed to lead, manganese, cadmium, copper, aluminum, etc. Because of the subclinical nature of most metal neurotoxicity, early detection programs are being explored to assess the risk factors in the perinatal, infancy, early childhood years, as well as adulthood and advanced age. In the communicative disorders a new method of assessing pitch perturbation in vocal signals has been developed which is stable across individuals, regardless of differences in fundamental frequencies; auditory processing deficits similar to those that occur in language-impaired populations have been found to occur also in groups of patients with no language, speech, or reading disorders; the finding has been made that the stimulants caffeine and dextroamphetamine have different effects on speech and language in normal adults; and a set of 12 objective acoustic measures of speech, timing, and coordination has been developed. Furthermore, recent discoveries about the production of peptides in neurotransmitters and neuroendocrine agents in the central nervous system have stimulated considerable basic research based not only on the traditional perception of the nervous system as a finely balanced electrical system, but also on the more recent perception that it is a very complex chemical factory as well. Since the nature of the biochemical abnormalities in genetically determined metabolic disorders of the nervous system has been discovered (the accumulation of abnormally large quantities of fatty material or carbohydrates due to a deficiency in the appropriate enzyme which is required for the normal disposal of the accumulating material), research on enzyme replacement therapy has been advanced with improved techniques to modify the blood-brain barrier, to target specific enzymes to the involved nerve cells, to develop diagnostic and carrier detection tests, and eventually to be able to insert the proper genetic messages into the appropriate cells in patients. Advances in medical and neurosurgical treatment of stroke have led to program development focusing on studies involving antiplatelet agglutination and surgical bypass clinical trials. The new chemical and immunological therapies for brain tumors are now emerging and as a result, tissue culture methods are being developed with promising potential for the treatment of these tumors.

The Institute will continue to give emphasis to research on ALS, health and spinal cord injury, MS, Huntington's disease, speech disorders, hearing impairments, etc., even though research leads are yet ambivalent.

Relevance to Broader Health Objectives

While maintaining a close watch on the evolving and rapidly growing field of neurobiology, NINCDS is planning extramural and intramural research efforts within the scope of its overall goal to (a) advance the frontier of knowledge in the prevention of disease, (b) communicate its basic and clinical research findings to the research and academic communities, and (c) expedite and facilitate the timely transfer of its research findings to the community of providers and consumers in the health care delivery system. A small cadre of highly skilled clinical investigators is exploring methods for the translation of the core of current and new information into clinically applicable modalities of prevention and therapy. The ultimate intent is to have research planning guided by enlightened societal needs and to monitor the research endeavor not only in terms of its process but also in terms of its effect and impact on the ultimate health status of the total population. In this way, research on the prevention of stroke, post-traumatic epilepsy, hereditary metabolic disorders, hearing loss, and environmental neurotoxicity, based on leads emanating from basic science, will have direct relevance to the broader objectives of reducing the costs of medical care and of human suffering, and improving the quality of a prolonged life. One of the challenges of neuroscience with far-reaching implications for disease, health, and social behavior is the understanding, in biological terms, of the higher mental processes such as learning, memory, attention, and decision-making. Studies in animals are beginning to throw light on some of these processes and conversely, recently established knowledge about cognitive processes in humans now permits further relevant studies in animals. The relevance to broader objectives is tremendous indeed.

NINCDS

FY 1981 Accomplishments

A number of important advances have been made in our understanding of the nervous and communicative systems and their disorders.

Stroke and Trauma Program

- The baseline patient data information derived from the comprehensive stroke centers has demonstrated that transfer of currently employed therapeutic modalities into the community does in fact have an effect on the outcome of morbidity and mortality of stroke patients over and above those resulting from programs of hypertension control.

- Recent research on the treatment of trauma patients has thrown much new light on secondary reaction of the spinal cord to injury, and on the effectiveness of currently available methods of diagnosis and treatment.

- PETT is opening new vistas of knowledge about facets of neurological disorders: cerebral metabolism; localization of functions within the brain; aging and senile dementia; glucose utilization in normal and disease states; the severity of a stroke lesion in terms of metabolic stages rather than only morphological appearance; the metabolic activity of malignant tissue within the brain; the effect of various modalities of tumor treatment; damage to the brain caused by Huntington's disease, Alzheimer's disease, and Tourette's syndrome; and the cerebral metabolism of patients with seizures between and during seizures.

Communicative Disorders Program

- Development of a new method for assessing pitch perturbation in vocal signals;

- Development of a set of 12 objective acoustic measures of speech timing and coordination (these measures differentiate between different forms of dysarthria, including hypokinesia in Parkinson's disease, Shy-Drager syndrome, buccofacial tardive dyskinesia, and Huntington's chorea); and

- Studies to resolve controversy about the efficacy of antihistamines, decongestants, adenoidectomy, and tympanostomy tube insertion in the treatment of otitis media with effusion.

Office of Biometry and Field Studies

- Several national probability sample surveys of neurological disorders (stroke, head, and spinal cord injury, and intracranial neoplasm) have been completed, and the results are being disseminated to health care providers;

- A statistical coordinating center for the conduct of clinical trials is being established to direct and support a study of manipulative therapy in sports medicine;

- A study of cognitive development in children treated with phenobarbital after an episode of febrile seizures;

- The field work for a study of senile dementia is being monitored in a cooperative study with NIMH and the Johns Hopkins University--final plans for implementation of a descriptive study of debilitating headache will be completed;

- A pilot study of epilepsy patients using anticonvulsive medication is being conducted; and

- Trend analysis based on reported mortality and morbidity data continues, with an increase in the number of neurologic disorders under study.

Neurological Disorders Program

- Program announcement soliciting applications in the area of motor neuron system degenerative diseases has been issued in an attempt to stimulate research into amyotrophic lateral sclerosis and other diseases characterized by premature death of neurons and degeneration of axons;

- A clinical trial of plasmapheresis in the treatment of infectious polyneuritis (Guillian-Barre Disease) has been initiated to determine if this treatment would reduce the duration and severity of paralysis which accompanies this disease;

- A program announcement has been issued soliciting research applications for program projects and centers to study Alzheimer's disease and related dementias;

- A program announcement soliciting research into the etiology and treatment of various movement disorders has been issued;

- A contract has been awarded to the Universidad de Zulia in Maracaibo, Venezuela, to study a concentrated focus of Huntington's disease in northern Venezuela, and two grants have been awarded to establish "Centers Without Walls" to support clinical and basic research aimed at discovering the etiology and pathogenesis of Huntington's disease and developing appropriate new physiological and sociopsychological treatments;

- The drug development program of the Epilepsy Branch has identified 11 promising chemicals with demonstrated antiepileptic activity in animals, and has selected three for toxicological evaluation, working closely with American pharmaceutical firms in selecting drug candidates for clinical trials;

- Research on multiple sclerosis is directed toward attempts to locate proteins which relate to the formation of myelin for the development of early detective and diagnostic tests for the disease;

- Consensus development conferences have been conducted on the treatment of febrile seizures in children and on Reye's syndrome (it was agreed by the Conference that prophylactic therapy [phenobarbital] should not be used unless there is evidence of neurological problems such as mental retardation and hydrocephalus or a family history of nonfebrile seizures; program announcements soliciting applications for research projects or centers to study Reye's syndrome and disorders of the neonatal brain have been issued); and

- The role of peptides in neurobiologic function has received increasing attention in recent years. At least 20 separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Receptors for many of these substances are now being searched for in brain tissue; pathways linking peptidergic systems are under investigation with neuroanatomical tracing techniques and immunocytochemistry, unraveling relationships with hormone secretion, sensory conduction, pain mechanisms, and behavioral responses.

Intramural Research Program

- The effect of the CNS on general immunological reactions of the body is under intense study;

- Laboratory studies will explore various chronic, progressive, and noninflammatory central nervous system disorders (such as Creutzfeld-Jakob disease) which now appear to be slow infections caused by transmissible viruslike agents;

- Another study will deal with the regulation and means of replication of viruses capable of producing encephalitis or meningitis;

- Other research efforts remain focused on how the central nervous system controls movement and on the neural basis for learning;

- Studies on new anti-Parkinson disease agents such as lisuride are gathering increasing evidence favoring the existence of pharmacologically distinct categories of dopamine receptors in the mammalian central nervous system;

- The NINCDS is initiating a program in clinical communicative disorders research with the opening of the Ambulatory Care Research Facility wing of the Clinical Center this year;

- Techniques have been developed for precise evaluation of neurological deficits such as tremor, clumsiness, and disturbances of gait; computerized methods are being employed for data storage, analysis, and retrieval to help determine the effectiveness of therapy. This approach may provide an important link between Parkinsonism and the normal process of aging of the nervous system;

- Persons affected with fatal diseases such as Tay-Sachs, Gaucher's, Fabry's, and Niemann Pick are receiving experimental therapy to metabolize fatty substances which accumulate in humans and lead to convulsive seizures and death, together with the further development of prenatal tests to diagnose these diseases;

- Work on the function of the ear will continue to be concentrated on neurotransmitter studies which show how sound messages are conducted to the brain;

- Followup studies on the Nobel Prize-winning research on slow infectious viruses will continue to involve intensive efforts to delineate the chemical nature of such viruses; and

- A program of biological, immunological, and chemotherapeutic investigations of human brain tumors has been launched; diseases of the nervous system may be the result of immune systems that are resistant to infectious agents, or are overreactive; immunology is a powerful tool to study normal and abnormal cells, carriers of disease, and the biology of neoplasms; this interplay between genetics and biochemistry has important potential to elucidate the underlying mechanisms and early detection modalities for preventive intervention in scrapie, Alzheimer's disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, lipoidosis, and tumors.

Fundamental Neurosciences Program

- The neural prosthesis program has reported major results in the development and fabrication of tantalum capacitor electrodes small enough for intracortical implantation; a theory has also been advanced about the auditory signal processing by the brain, which can be tested after electrode arrays have been fabricated; the testing of multichannel auditory prostheses in deaf individuals is also being continued;

- Investigations of neuroanatomical asymmetry in the human temporal lobe and related psychological characteristics are continuing; and

- Studies on the very exciting areas of local neuronal interactions are progressing, with new insights available this year.

FY 1982 Program Changes

- FY 1982 will be the third year for the implementation of the National Research Strategy for Neurological and Communicative Disorders. This plan incorporates significant new initiatives with emphasis proposed in the following areas: (a) CNS plasticity, developmental neurobiology and cell proliferation and migration, dendritic development, synaptogenesis, cell susceptibility to insult; (b) pathophysiology and etiology of the most common disorders of the developing nervous system; (c) the nature, neural mechanisms, causes, and remediation of chronic destructive pain of diverse origins, and the neurochemistry of opioid peptides; (d) human communication and its disorders, including hearing, speech, and language; (e) viral and infectious agents, including "slow" virus and unconventional virus agents and their possible link to etiology, and neurochemistry and pathophysiology of a range of degenerative chronic neurological disorders, e.g., Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease; (f) immune factors in neurological disease, endocrine and hormonal abnormalities, and other endogenously or possibly genetically caused disorders of the nervous and neuromuscular systems; (g) changes in CNS metabolism and biochemistry as a consequence of trauma and stroke, and development of diagnostic and interventive techniques to avoid permanent tissue damage and aid restoration of function; (h) mechanisms of axonal transport and chemical factors influencing nerve growth and regeneration; (i) neuronal structure and function and potential prognosis for differing treatments through the use of PETT; (j) detection, diagnosis, and treatment of CNS neoplasms; and (k) neurophysiological and neurochemical correlates and bases of complex human behaviors including memory, appetite, emotion, language, and higher cognitive functions.

- Institute plans include additional new and competing National Research Service Awards, with emphasis on clinical research in neuroimmunology, neurovirology, neuroendocrinology, otolaryngology, speech and language pathology, and spinal cord injury and regeneration.

- The Intramural Research Program (IRP) will receive additional funds for "Other Objects" and positions to compensate for decreases in the past and to provide for the establishment of its PETT research program and for clinical research facilities in otolaryngology. It is also planned to maintain the present research effort by providing sorely needed positions and funds in medical neurology, surgical neurology, neuroimmunology, and molecular genetics.

- Support of research on CNS regeneration as a possible means of restoring function after injury will be enhanced. A clinical trial is being planned to study the effectiveness of Naloxone in the treatment of acute spinal cord injury.

- Expanded support is also planned for studies proposed by the three commissions and the Congressional directives aimed at the control of Huntington's disease, epilepsy, and multiple sclerosis.

- Support for initiatives in the area of human communication and its disorders, including hearing, speech, and language, will be provided. Continuing progress is expected in the development of sensory aids for the deaf, an improved understanding of the effects of noise on hearing, in new knowledge of the brain organization underlying language functions and speech pathology, and in prevention of hearing loss resulting from otitis media in children.

- The plan also allows for the continuation of initiatives in fundamental neurosciences research. Significant advances are expected in our understanding of how information is transferred to and between brain cells and stored, of interactions between neurones, and of the significance of brain asymmetry.

FY 1983 Program Changes

- NINCDS plans to emphasize clinical research training, particularly in selected areas of national shortage, e.g., CNS trauma.

- In the Intramural Research Program (IRP), the Institute proposes to establish a Laboratory of Communicative Disorders which will investigate the clinical problems of the ear and the larynx. NINCDS also plans to go forward with the development of the PETT research program. For both these activities, seven staff positions will be required. Further, it is necessary to maintain IRP as a unique resource of scientific excellence in neurological and communicative sciences by providing the required positions and funds to carry out its activities.

- The PETT program has started producing provocative data as reported above. These observations will be expanded further to provide a better understanding of the metabolic basis for the neurological and communicative disorders.

- In the area of peptide receptors and peptidergic pathways in CNS, important advances will require detailed analyses of the (a) neuroanatomy, (b) neurophysiological effects of peptides and a definition of their sites of action, (c) neuropharmacological studies to identify receptor sites on neural tissue and to identify agonists and antagonists that might have therapeutic implications, (d) hormonal and cerebral spinal fluid distribution and effects of peptides, and (e) behavioral effects induced by these substances.

- In addition, there are a number of research areas of special interest to the Congress. This has been manifested by the introduction of legislation and the establishment of several commissions. Because of this, there is likely to be considerably increased interest in the areas of spinal cord injury and regeneration, communicative disorders, neurogenetic disorders, and Reye's syndrome.

Potential Impact of Program Changes on Three-Year Period (1983-1985)

These impact changes emanate directly from research leads and program changes during FY 1981 and FY 1982 and encompass either the development of further research leads or the emergence of various findings and technologies that lend themselves to intervention modalities in the prevention of some of the major chronic diseases of the nervous system:

- In the communicative disorders area NINCDS expects to see increased sophistication in sensory aids for the deaf, improved understanding of the effects of noise on hearing, enhanced knowledge of the brain organization underlying language functions, and refined methods for the early detection of speech misarticulation and stuttering in children and for the prevention of hearing loss resulting from otitis media in children.

- The proposed budget for FY 1982 would allow further development of grant-supported Comprehensive Stroke Centers by 1983, of Comprehensive CNS Trauma Centers by 1984, and of Comprehensive Coma Centers by 1985; thereafter, local resources would assume a major part or all of the funding responsibilities for the public information aspects of these centers. The grant-supported spinal cord regeneration research program would also continue its orderly growth for the study of the regeneration potential in the damaged human nervous system. The PETT program would likewise be supported and its research applications explored and demonstrated with manifold basic knowledge enhancements in every program area of the Institute.

- The proposed budget would allow NINCDS to proceed with synthesis, animal screening, clinical testing and development of antiepileptic drugs. The program would continue to implement the recommendations of the Commissions on Epilepsy and on Huntington's disease. Increased understanding is expected to be achieved in the events of neurobiological development, timing of insult in determining the nature of neuronal disruption, and the processes of demyelination and degeneration. Research in fundamental neurosciences will lead to an enhanced understanding of basic problems, e.g., how information is transferred between brain cells and stored, local neuronal interactions, and the significance of brain asymmetry. It is expected that recently developed knowledge relating to the understanding of the basic principles underlying neural prosthesis will be increasingly utilized.

- The establishment on the NIH campus of a model intramural clinical research team with expertise in otolaryngology, audiology, and the speech and language sciences is planned with the opening of the Ambulatory Care Research Facility. NINCDS is also the focal point for the planning of the collaborative project with the Clinical Center, National Institute on Aging, and National Institute of Mental Health to install an intramural PETT facility equipped with a cyclotron. This expanded research facility will enable the Institute to investigate, in basic and clinical research, a number of areas in neurological and communicative disorders which may be considered as gaps in extramural scope of research; such facilities will emphasize the development of programs relevant to the interest of the community of communicative sciences and will widen the opportunity for trans-NIH collaboration in clinical research.

MEMORANDUM

NINCDS
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Acting Director
National Institute of Neurological and Communicative
Disorders and Stroke

DATE: FEB 1 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It is gratifying to note the important advances that have been made in our understanding of the nervous and communicative systems and their disorders. It is clear that the field of neurobiology offers exciting opportunities for increasing further our knowledge in this area. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

D S Fredrickson
Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

Important advances have been made in understanding the nervous and communicative systems and their disorders including studies on the mechanism of action of the nerve growth factor in central nervous system (CNS) regeneration, and the use of the PET (positron emission tomography) technique for important studies of cerebral metabolism such as localization of glucose utilization within the brain in aging and senile dementia. Progress is expected in the development of sensory aids for the deaf, in increasing understanding of the brain organization underlying language functions and speech pathology, and in preventing hearing loss resulting from otitis media in children.

Impact of Stabilization

- The number of competing research project grants (R01s) to be supported in 1981 and 1982 will decrease slightly from the level supported in 1980.
- The number of program projects to be supported in 1981 and 1982 will increase somewhat over the 1980 level.
- There will be a modest reduction in the number of research centers supported in 1981; under the 1982 planning assumption the number of research centers will be held at approximately the 1981 level.
- Research and development contracts will decline appreciably in 1981 and 1982. This will delay efforts in the neural prosthesis program and the drug development activity.
- Intramural research will remain relatively stable in 1981 and 1982. The number of positions will remain constant during this period. This will not permit adequate development of the PET research facility and will delay the establishment of a clinical research program in otolaryngology.
- Support for training in 1981 and 1982 will remain essentially at the 1980 level. Slight increases in institutional awards will be offset by slight decreases in individual awards. The NINCDS considers these levels to be far below the levels required to meet perceived needs.

Personnel

- A lack of positions has prevented the Institute from capitalizing fully on scientific opportunities.

- The Institute is exploring possibilities that may exist for greater use of visiting fellows, special experts, and similar mechanisms.

Training

- The overall level of training has declined steadily since 1973.

- The number of M.D.'s entering research training has decreased significantly in recent years.

- The NINCDS has given special emphasis to institutional clinical research training grants designed to attract M.D.'s to research, and the Institute will expand a program of Teacher Investigator Development Awards to help establish young clinical investigators.

Opportunities

If increases in funds become available in FY 1983, some of the research opportunities that will be explored include:

- Application of the PET technology to provide a better understanding of the metabolic basis for neurological and communicative disorders.

- Studies of peptide receptors, including investigations of the neurophysiological effects of peptides, identification of receptor sites in neural tissue, and characterization of compounds that might have therapeutic implications for neurological and communicative disorders.

- Expansion of studies in neuroimmunology.

- Basic and applied studies of spinal cord injury and the processes involved in neural regeneration.

- Implementation of studies called for by the Congress in the areas of epilepsy, multiple sclerosis, Reye's syndrome, and Huntington's disease and other neurogenetic disorders.

- Full development of an intramural clinical program in the communicative disorders.

Establishment of Clinical Investigators in the Neurological and Communicative Sciences

Informed sources, including the National Academy of Sciences, the NINCDS National Advisory Council, and academic leaders in the neurological and communicative clinical sciences, report that there is a serious shortage of clinical investigators in these disciplines. They also report a continuing decline in both the absolute number and the relative proportion of capable young clinicians entering research training. Unless this trend is reversed, important areas of clinical investigation will be neglected.

One reason for this problem is that with the clinical demands of medical training, internship, and residency, it is impossible to provide time for adequate research training. In addition, the rewards of clinical practice versus a research career are such as to make research training unattractive. Because of this lack of training, it is very difficult for the clinician to compete successfully with Ph.D.'s who have had several years of research training and experience. Also, since presently there is little assurance of support for research training and development and for a productive career in clinical research, this career objective competes poorly for the attention of young clinicians.

A multifaceted approach to the problem is necessary. Stabilization of the research grant program will tend to give some assurance of support for a career in clinical research. The NINCDS is giving special attention to the funding of institutional and individual training awards in clinical research areas of Institute responsibility. In the case of Career Development Programs, every effort is being made to see that young clinical investigators are being given every consideration in the competition for available funds. As part of this activity, NINCDS maintains a program of Teacher Investigator Awards (comparable to Research Career Development Awards) designed especially to develop and establish young clinical investigators. The candidate need not have more than three years of postdoctoral experience, and a good deal of weight is given to the candidate's research potential rather than to his or her research achievements.

Intramural Research Program
Initiatives in Otolaryngological Research and Positron Emission Tomography

Previous discussion emphasized the need for a targeted research effort in the clinical communicative sciences. Discussion below (1) summarizes the efforts of NINCDS to stimulate research in this field, (2) describes the immensity and importance of the clinical problems, and (3) refers to Congressional interest in this area. The community of otolaryngological scientists is greatly troubled about the paucity of research in their area of interest and recently met with the Director, NIH, about the problem.

As one step toward resolving this situation, two years ago NINCDS established a basic research Laboratory of Neuro-Otolaryngology in the IRP. However, this was an initial effort to meet this need. The Institute now proposes to continue its IRP development in this area by establishing a clinical research Laboratory of Communicative Disorders which will investigate clinical problems of the ear and larynx.

The exciting developments in positron emission tomography (PETT) have been summarized earlier in this presentation as one of the most promising research methods for the study of cerebral metabolism and need not be repeated here. Suffice it to say that the availability of an effective noninvasive technique that can detect small normal and abnormal metabolic changes in localized areas will provide exciting new opportunities for research on the brain and spinal cord. Therefore, NINCDS plans to go forward with the establishment in IRP of a Positron Emission Tomography Research Program. It must be recognized that both the establishment of the facility and the assembly and maintenance of the large highly specialized staff required will be very costly. However, there is no question that the scope and significance of the research opportunity fully justifies the cost.

Research Areas of Special Sensitivity

Spinal Cord Injury and Regeneration

Previous suggestions that a major cause of secondary injury following spinal cord injury could be the release or accumulation of norepinephrine at the site of injury have not been confirmed. Turnover studies have demonstrated a reduction in the activity of the membrane-bound enzymes tyrosine hydroxylase, dopamine beta-hydroxylase, and mitochondrial monomine oxydase. These changes resulted in an accumulation of dopamine and no change in norepinephrine concentration. This suggests that the changes in catecholamine metabolites after spinal cord injury simply reflect the disruption of function of membrane-bound enzymes and, therefore, are not important to the subsequent development of degenerative changes. Localized spinal cord trauma causes decreased blood flow throughout the CNS, particularly in the cord. The mechanismis unknown. The combined effects of low flow rates and presumably low perfusion pressure plus obstruction of the microcirculation could cause ischemia sufficient to produce irreversible changes in spinal cord axons. No improvement was seen in animals that received mannitol following injury. In the case of DMSO, 7 out of 20 animals (35 percent) showed some return of neurologic function.

A double blind randomized collaborative clinical trial to study the effects of corticosteroids on spinal cord injured patients is under way. A new approach is a clinical trial of naloxone on spinal cord injury.

In regard to neural regeneration, it is now well recognized that the neurons and axons of the transected or traumatized spinal cord in higher animal species can produce sprouts that initiate the process of regrowth toward target axons. Grafts of fetal rat brain will regenerate and reinnervate damaged regions of the brain. Recent research has demonstrated the existence of several nerve growth factors of distinctly different chemical structures and neurogenic specificities. Despite these important developments, most of the research must continue at the basic science level until more promising approaches are opened up. NINCDS presently supports research in the area in the amount of approximately $8 million per year.

Communicative Disorders

The NINCDS has made repeated efforts to stimulate research on the communicative disorders even before publication of the report, "Human Communication and Its Disorders--An Overview," in 1969. Subsequently a program of Outpatient Clinical Research Centers was developed, particularly for investigators in the communicative sciences. Many announcements were published inviting applications for research and research training grants. More recently an effort has been made to show leadership in the Intramural Research Program in the establishment of the Laboratory of Neuro-Otolaryngology and the proposed Laboratory of Communicative Disorders.

The most urgent need is for trained research personnel. Competent investigators presently in the field must be assured that research support will be available. Efforts to encourage young clinical investigators as described above will be helpful in increasing the number of otolaryngologists in research.

Reye's Syndrome

An International Conference on Reye's syndrome (RS) was held in Halifax, Nova Scotia, on June 22-23, 1978, sponsored by NINCDS and several Canadian and voluntary agencies. It was clear that additional research was greatly needed. A joint (NINCDS, NIAID, NIADDK, NICHD) request for applications was published in the "NIH Guide for Grants and Contracts" on May 16, 1980. As a result of this request, NINCDS received three applications, which were acted upon by the National Advisory Council in January 1981. However, on the basis of scientific merit, one application has been recommended for disapproval and the other two have priority ratings much too poor to fund. Six more applications have been received, to be considered by the Council in May 1981. Finally, an NIH Consensus Development Conference on "The Diagnosis and Treatment of Reye's Syndrome" was held March 2-4, 1981.

There has been considerable constituent and Congressional pressure to expand research on RS. Senator John Melcher submitted a bill (S. 1794) providing for increased and more coordinated research. The essence of this bill was added as a House Amendment to S. 988, "The Health Sciences Promotion Act of 1980." It calls for the establishment of an RS Coordinating Committee with authority to award grants and contracts and to support two comprehensive RS treatment and diagnostic centers. However, it is felt that a planned gradual expansion of research in this area as new leads and more trained investigators become available would constitute a more effective attack on this problem than segregating this research under a separate bureaucratic mechanism.

Huntington's Disease and Other Neurogenetic Disorders

In October 1977, the Commission for the Control of Huntington's Disease and Its Consequences submitted its report including 27 recommendations, 13 of which are the primary responsibility of NINCDS. Most of these have been implemented, including the establishment of two "Centers Without Walls" involving the expenditure of some $5 million over a period of five years. For FY 1981, it is estimated that research on Huntington's disease and related areas will amount to approximately $14.6 million. This includes research on related genetic disorders as recommended by the commission. Also as recommended by the commission, a study of a special population of Huntington's disease families around Lake Maracaibo in Venzuela is under way. All these families are believed to be descendants of one individual, which makes them especially useful for linkage studies.

The replacement of glucocerebrosidase in Gaucher's disease and Fabry's disease has been eminently successful. The clinical course of the disease was greatly improved in two young boys. In two adult patients the accumulated hepatic glucocerebroside was reduced by 47 percent and 30 percent respectively. Also, enzyme replacement was well tolerated and none of the patients developed antibodies to the exogenous enzyme.

Methods have been developed for the purification of sphingomyelinase, the enzyme lacking in Nieman-Pick disease, obtained from human placental tissue like the other enzymes. It is difficult to obtain sufficient quantities of this enzyme for replacement therapy trials. However, a strain of Balb/c mice has been discovered with an autosomal recessive neurological degenerative disorder characterized by the accumulation of several sphingolipids. These animals exhibit a persistent deficiency of sphingomyelinase and glucocerebrosidase that is evident immediately after birth. This will be a very important animal model for enzyme replacement studies.

The previous prediction that the myelin-associated glycoprotein may be early involved in the destructive process in multiple sclerosis has received extraordinarily strong confirmation. This glycoprotein was found to be highly antigenic, and high antibody titers were raised to it. The antibody was used for immunocytochemical localization of the myelin-associated glycoprotein. It was found to be located between the axolemma and the inner part of the myelin sheath. In tissue sections from brains of MS patients, this glycoprotein is the first detectable brain component to disappear at the periphery of the expanding MS plaque. The destruction of this compound occurs even in areas of the brain that appear histologically normal. The high susceptibility of myelin glycoprotein to breakdown under these conditions suggests that it is likely to be intimately involved in the pathogenesis of multiple sclerosis.

PROGRAM PERFORMANCE SUMMARY

ANTIEPILEPTIC DRUG DEVELOPMENT PROGRAM

Program Description

Problems Addressed and Program Development

Two million Americans, approximately one percent of the population, have epilepsy, one of the most prevalent neurological disorders. Two hundred thousand Americans have seizures more than once a month. In addition, epilepsy is a disorder beginning in the pediatric age group; 75 percent of all patients with epilepsy have their first seizure before they are 18 years old.

A variety of treatments have been tried for epilepsy, but the first effective antiepileptic drug was potassium bromide, discovered more than 100 years ago. The modern era in antiepileptic drug therapy began with the use of phenobarbital in 1912. In the next 35 years about 50 other barbiturates were marketed, and many of these were tried for epilepsy. Phenytoin, the first nonsedative antiepileptic drug, was discovered through experiments with animals in 1937. Between 1938 and 1960, considerable progress in the search for new antiepileptic drugs led to the marketing of 13 such drugs. From 1961 to 1973, however, only one additional antiepileptic drug--diazepam--was marketed. Its use is largely relegated to the treatment of the rather infrequent but serious condition of status epilepticus. The development of new drugs for epilepsy diminished in part because of the impact of the Kefauver-Harris Amendment in 1962 and its financial implications for the pharmaceutical industry. This law, an outgrowth of the thalidomide disaster, required proof that a drug was efficacious as well as safe. The legislation appeared to have had an impact on drug development for disorders that affect relatively few people. The market for these drugs is thus limited and the return of corporate investment doubtful.

The difficulty of proving the clinical efficacy of antiepileptic drugs presented additional problems. One of these is the question of appropriate patient populations for controlled clinical trials: Do these populations exist? Must poorly controlled patients be studied? Clearly, it is unethical in the testing of a new drug to remove a patient's previously prescribed antiepileptic drugs so that seizure severity or frequency increases. Further, the major determining factor of the appropriate drug is the patient's seizure type, which may be difficult to identify. Epilepsy is a heterogeneous syndrome, and seizure classification must be carefully defined for each drug study. Also, the seizure frequency must be measurable; efficacy of a new drug is usually determined by a decrease in seizure frequency. All of these factors contributed to the reluctance of pharmaceutical firms to pursue the development of new antiepileptic drugs in the period 1961 to 1973.

A survey of pharmaceutical firms conducted for the U.S. Surgeon General's Public Health Service Advisory Committee on the Epilepsies in 1966 revealed that many firms had no new antiepileptic drugs under development for marketing, since several of their drugs had not gained new drug approval because of inadequate proof of efficacy.(1) The single most frequent reason cited for lack of interest in antiepileptic drug development was financial: the cost of development was prohibitive compared with the expected return from marketing.

The Epilepsy Branch (then Section on Epilepsy) was formed in 1966 partly in response to these problems.(2) It began investigations of methodology in 1967, clinical trials in 1969, and preclinical screening of anticonvulsant compounds in 1975. In 1977 the Congressionally established Commission for the Control of Epilepsy and Its Consequences (3) recommended continued Federal funding for NINCDS new drug development, and advised the expansion of "animal screening for potential drugs" and the "evaluation program for new drugs." In 1979 the Panel on Convulsive and Neuromuscular Disorders (4) listed "Development of new and improved therapeutic agents and techniques and a framework for evaluating clinically the therapeutic potential of such agents and techniques" as one of the three highest priorities for investigation into the epilepsies.

The initial work of the Epilepsy Branch emphasized identification of seizure types. A series of methodological advances followed, especially the now widely accepted intensive monitoring system employing video recording and telemetered electroencephalography. These advances were utilized in studies initiated by the Epilepsy Branch that ultimately led to the Food and Drug Administration (FDA) approving four new antiepileptic drugs: carbamazepine in 1974, clonazepam in 1975, valproic acid in 1978, and clorazepate in 1981, the latter approved for adjunctive treatment of epilepsy.

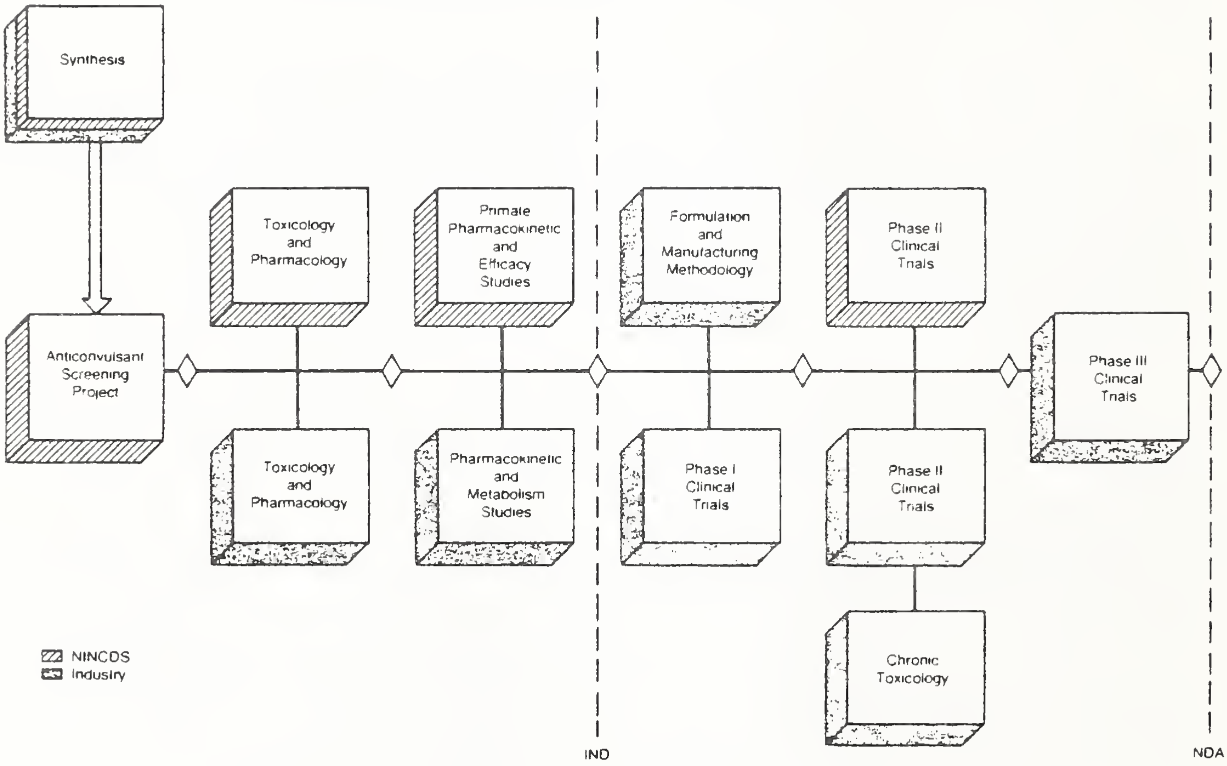
Until 1975 the NINCDS drug development effort was limited to drugs which had been previously marketed in other countries. In that year, it became apparent that the United States could no longer depend solely on the development of drugs available in foreign countries, and involvement would be necessary at a stage before clinical trials. Investigations to determine why preclinical antiepileptic drugs were not available for development revealed both financial reasons for pharmaceutical firms and the lack of access to early anticonvulsant pharmacological testing for academic medicinal chemists. To help alleviate these problems, an anticonvulsant drug screening project was begun in 1975 and a toxicity project in 1980. When a compound appears outstanding in the later phases of the screening project, pharmaceutical firms are urged to make a financial commitment to major toxicology and pharmacology tests in collaboration with the toxicology project of the Epilepsy Branch; academic suppliers are assisted in finding sponsors. The Epilepsy Branch also has a small grant project for chemical synthesis of new compounds. The grantees send the synthesized compounds to the screening project for evaluation. Another important part of the NINCDS drug development program is the primate model of partial seizures in monkeys. It allows the testing of new drugs in a near imitation of certain types of human seizures.

The Antiepileptic Drug Development Program of the Epilepsy Branch has anticipated possible legislation on "orphan drugs" by more than a decade. Recent Congressional hearings have emphasized the need, especially where appropriate models are available, for programs evaluating new drugs for "orphan" diseases, so called because the financial return on drugs for treatment of these diseases is inadequate. Also a GAO report dated July 17, 1981, to Representative Henry Waxman, Chairman, Subcommittee on Health and the Environment, Committee on Energy and Commerce, indicates continuing concern for drugs of little commercial value and suggests that government-supported drug development is appropriate in certain areas.

Current Program Organization and Resources

The clinical and preclinical portions of the Antiepileptic Drug Development (ADD) Program are summarized in the diagram below.

THE ANTIEPILEPTIC DRUG DEVELOPMENT PROCESS


Synthesis
Anticonvulsant Screening Project
Toxicology and Pharmacology
Toxicology and Pharmacology
Primate Pharmacokinetic and Efficacy Studies
Pharmacokinetic and Metabolism Studies
Formulation and Manufacturing Methodology
Phase I Clinical Trials
Phase II Clinical Trials
Phase II Clinical Trials
Chronic Toxicology
Phase III Clinical Trials
▨ NINCDS
▩ Industry
IND
NDA

Staffing and funding of the ADD Program for 1978 to 1982 are summarized in Table 1. The staff consists of 14 individuals in pharmacology, pharmacokinetics, neurology, drug regulation, biostatistics, pharmacy, and related supporting positions.

Table 1

Staffing and Funding, ADD Program, FY 1978-82
(Dollars in Thousands)

	1978	1979	1980	1981	1982 est.
Personnel	12	13	14	14	14
Direct operations	$ 203	$ 271	$ 337	$ 300	$ 297
Contracts	$1,167	$1,317	$1,382	$2,134	$2,304
Grants	$ 54	$ 500	$ 530	$ 562	$ 737*

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*Includes $600 for cooperative agreement on antiepileptic drug prophylaxis of seizures following head injury.

The conduct of a drug development program places many demands on staff personnel. The review of grants, site visits, contract monitoring, program planning and evaluation, and other functions all require considerable staff support. Most of the above staff members perform functions in the Epilepsy Branch aside from drug development. Furthermore, much of the direct operation serves needs beyond drug development.

Program Objectives and Activities

Program Objectives

The primary objective of the ADD Program is to facilitate the development of antiepileptic drugs that are efficacious against all types of seizures with minimal side effects. The achievement of the primary goal requires several steps involving the following immediate goals: (a) synthesis, (b) anticonvulsant identification, (c) anticonvulsant quantification in several species and by several routes of administration, (d) profile of toxicity in several species, including chronic administration and tolerance, (e) anticonvulsant effectiveness in animal models of seizures, (f) initial administration to humans, (g) determination of antiepileptic effect in humans, (h) human pharmacokinetics, (i) controlled clinical trials, and (j) long-term followup.

Epilepsy represents a unique disorder of brain function through which information on normal brain function can be obtained. Antiepileptic drugs have been developed empirically, and only recently has some progress been made in determining their mechanism of action on the brain. As these studies proceeded, more has been learned about the function of the brain itself and perhaps will allow us to predict which drugs will be most effective in controlling brain abnormalities. Thus, secondary or long-term objectives of the ADD Program are (a) increased understanding of normal brain function, (b) enhanced knowledge of the epileptic discharge and its effect on normal brain function, (c) further understanding of mechanisms of actions of antiepileptic drugs as related to their structure and application of this structure-function relationship to development of more effective drugs, (d) development of new procedures to facilitate the determination of antiepileptic drug effectiveness, such as new animal screening procedures, (e) development of methods to increase effectiveness in all phases of drug testing, particularly for central nervous system (CNS) drugs, and (f) development of more effective protocols for ethical testing of drugs in humans to allow rapid availability of effective drugs and to assure exposure of a minimal number of individuals to ineffective drugs.

The ADD Program also has two tertiary objectives. First, as new drugs become available and as new testing techniques are developed, this information must be transferred to the medical community as rapidly as possible. Second, it is important to recruit and train scientists in central nervous system research.

Current Program Activities

Program activities first began in the area of controlled clinical trials and have focused on the design, monitoring, and analysis of such trials. From 1970 to the present, the Branch has conducted controlled clinical trials of drugs for the treatment of absence seizures (three trials), generalized tonic-clonic or complex partial seizures (seven trials), the prophylaxis of posttraumatic epilepsy (two trials), and infantile spasms (one trial). This year the Program began two controlled trials of new drugs in complex partial seizures and infantile spasms.

Since 1975 the ADD Program has attempted to stimulate development of drugs prior to the clinical trial stage. Grants and contracts have been awarded for chemical synthesis of novel compounds. The screening project has been developed to obtain compounds from multiple sources and to assure that the drugs will be carefully and rapidly evaluated through all phases of screening. In this project the program staff carefully monitors a seven-phase screening of compounds for anticonvulsant activity, participates in development of new animal models for testing, and evaluates results to select compounds for retesting or advanced screening. Following screening, selected compounds are subjected to 90-day toxicity evaluation in the rat and dog. Some are evaluated for safety and efficacy in the primate seizure model. Investigations of human pharmacokinetics have necessitated development of analytical methods for determination of new drugs in body fluids, correlation of plasma drug concentration with efficacy and toxicity, development of methods to assure adequate laboratory quality control, and collaborative development of drug reference standards.

The ADD Program has developed objective monitoring techniques for use in clinical trials and has assisted in the transfer of this technology to the clinic. Scientists are continually being recruited and trained in the Program, and most have pursued careers in the neurosciences. Several Program-trained scientists from other countries are now working worldwide on the problem of epilepsy.

Evidence of Program Performance

Despite complex responsibilities and many constraints, the ADD Program has been very productive. Examples of accomplishments include:

- Developed a system for the intensive monitoring of patients with seizure disorders to precisely determine seizure type. This approach to patient monitoring has been adopted throughout the world.
- Participated in clinical research which led to the approval of four new antiepileptic agents, now used by approximately 400,000 Americans.
- Stimulated the interest of medicinal chemists in the pharmaceutical industry and in the academic community to create novel compounds. The ADD Program screens these chemicals for activity and evaluates the most promising ones more extensively.

External Program Evaluation

The Director, Neurological Disorders Program, more than a year ago, initiated an external review of the ADD Program, which is to take place early in 1982. An ad hoc review group was selected by a consultant, a chairman was chosen, and preliminary background information was furnished.(5) The members consist of two academic and clinical neurologists, three academic pharmacologists, two pharmaceutical industry pharmacologists, and a pharmacologist from the U.S. Army drug development program. A two-day evaluation will take place on-site in 1982.

Objective performance evaluation of the ADD Program may be obtained from three advisory groups. The Epilepsy Advisory Committee,(1) the Panel on Convulsive and Neuromuscular Disorders in the National Research Strategy,(6) and the Commission for the Control of Epilepsy and Its Consequences(3) together have made 47 recommendations relating specifically to the ADD Program. Their implementation is shown in Table 2.

Table 2

Advisory Group Recommendations to ADD Program

	No. of recommendations	Fully implemented	Partially implemented	Not implemented
Advisory Committee	5	3	2	0
Panel	24	11	12	1
Commission	18	9	8	1

Internal Program Evaluation

Performance may be assessed on the basis of three fundamental evaluation processes suggested by Barkdoll(7): (a) the measurement of the impact of the program, (b) the measurement of the efficiency of the program in reaching its stated objectives, (c) the testing of alternative strategies to reach program goals more effectively. Each of these processes may be applied to the ADD Program in assessing its performance in relation to the overall mission of the Epilepsy Branch in improving the diagnosis, treatment, and prevention of the epilepsies. An example of each measure of evaluation will be cited.

The impact of the ADD Program may be evaluated by assessing the utilization of new drugs made available through the Program-sponsored clinical trials. Three antiepileptic drugs, carbamazepine (Tegretol), clonazepam (Clonopin), and valproic acid (Depakene), were marketed in the U.S. in 1974, 1975, and 1978, respectively. Since no new antiepileptic drug had been marketed since 1960, the availability of these new drugs is in itself evidence of Program success. Further evidence is provided by the National Disease and Therapeutic Index, a monthly survey of patient-physician contacts, which indicates current antiepileptic drug usage. Their data show that in 1980, 12 percent of epileptic patients in the U.S. received carbamazepine, 10 percent received valproic acid, and 1 percent received clonazepam. Thus, more than 20 percent of the patients with epilepsy--approximately 400,000 Americans--are benefiting from drugs made available because of the support of the ADD Program. A fourth drug, clorazepate, was approved as an adjunctive treatment in 1981; data about its use in epilepsy are not yet available.

The efficiency of the ADD Program may be evaluated by reviewing the anticonvulsant drug screening project, a key component of the Program which identifies chemicals for possible further development. This project may be evaluated by analyzing the effectiveness of accessioning compounds and the proportion of which are worthy of further testing. Table 3 indicates that an increased number of compounds was acquired in the last two years; the trend continues in 1981. The annual number of suppliers of compounds is relatively constant. The screening project has developed so that the capacity of the contractor has virtually been reached. An increase of 10 percent could be accommodated, but a greater increase would require the addition of a second contractor.

Table 3

Anticonvulsant Drug Screening Project of the ADD Program

Year	No. of new compounds received	No. of suppliers*	No. of screened compounds considered for toxicity evaluation**
1975	744	44	NA
1976	737	47	NA
1977	432	35	NA
1978	576	60	NA
1979	802	59	NA
1980	1,013	53	14

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*Cumulative total for 1975-1981 is 165.
**Toxicity project was started in 1980.

Finally, alternative strategies in the ADD Program can be tested to see whether they might be more fruitful than those currently being followed. For example, in screening of new compounds for possible anticonvulsant activity in acute animal models which are sensitive to known effective drugs, the methodology has been meticulously and successfully worked out by a senior expert at the University of Utah. These screening techniques have a long tradition and are widely used in the pharmaceutical industry. In order to test alternative strategies, the Program invited a consultant to criticize its procedures. This expert, formerly with the pharmaceutical industry and now Dean of Science at Rensselaer Polytechnic Institute, articulated an objection to the Program's screening methods; that is, the current strategy will reveal new compounds with the same activity as drugs already known. If the objection is correct, which seems unlikely, a truly different "breakthrough" drug might therefore be missed. The Program is testing this alternative strategy. Some of the compounds rejected by the standard screen are being rescreened with a new model based on recent neurochemical theory. Those found particularly active will be tested further, in the hope of identifying compounds that are different in action and effective in intractable seizures.

Major Issues or Problems Cited by Organizations Within the Administration, Congressional Committees and Organizations (GAO, CBO, CRS, OTA), and Interest Groups

Organizations within the Administration, Congressional committees, and organizations or interest groups have cited no issues or problems related to the ADD Program. There is a concern at the Congressional level about the general lack of drug development for those products with small markets and thus little commercial appeal. This problem has been repeatedly recognized, most recently in a GAO report.(8) The Pharmaceutical Manufacturers Association formed a committee in 1981 to investigate and respond to the "orphan" drug problem.

Barriers and Issues Relating to Program Performance

One of the most important barriers to any drug development program is the limitation of the models. The animal models of epilepsy used to screen compounds for anticonvulsant activity have disadvantages as well as advantages. They are valuable in separating fundamental seizure types, yet their relevance to human epilepsy is indirect. Drug activity in these acute experiments does not necessarily mean therapeutic usefulness in humans. Long and expensive trials are necessary to reveal whether the antiepileptic potential can be realized in humans. It is hoped that grant-supported research will lead to improved models of seizure disorders.

New compounds may be difficult to obtain. A very large increase in the number of compounds screened, e.g., from the present 1,100 to 10,000 a year, might increase the yield of new antiepileptic drugs. Unfortunately, the proportion of active compounds varies with the suppliers. The Epilepsy Branch has developed the capability of evaluating suppliers as well as compounds. An increased pool of compounds requires not only money to screen them but judgment about their potential.

Another barrier is the time, complexity, and expense of toxicological and pharmacological evaluation. Contemporary standards for drug development include a number of expensive toxicological tests in animals. Before a new drug is approved for national distribution, the state of the drug-testing art requires 1- to 2-year trials in at least two animal species. The trials must be meticulously carried out, and the cost is $250,000 to $700,000 each. Other tests involve studies of carcinogenicity effects on reproduction and embryonic development, effects of formulation on absorption and metabolism, and possible specific organ toxicity. Support for such tests is especially difficult for the noncommercial sponsors, who supply 60 percent of compounds to the ADD Program.

The disorder of epilepsy itself creates difficulties in establishing the safety and efficacy of new drugs. Many types of uncontrolled seizures are uncommon, so that a test population is difficult to assemble. In addition, the disorder varies greatly from patient to patient, and diagnostic criteria cannot be generally applied. Clinical trials of antiepileptic drugs, therefore, must often be lengthy and extremely detailed if results are to be credible and conclusive. This is in contrast to trials of drugs in many other conditions, such as pain or infection, which are usually of limited duration.

Coordination with other organizations can be a problem. Coordination of Government-sponsored research with regulatory review requirements, or with the needs of commercial sponsors of new drugs, continues to be challenging. The ADD Program has thus far been quite successful in dealing with most such problems.

A further barrier to the ADD Program occurs when the Government is not able to hire outstanding personnel. Depth and breadth of experience are implicit in developing new drugs, and lack of experts can be a problem. Fortunately, the Epilepsy Branch has been successful in recruiting and retaining an unusually broad and experienced staff. It is not, however, expert in all aspects of drug development (e.g., in medicinal chemistry or synthesis). The personnel policy that limits hiring to persons already employed by the Department may hinder future recruitment efforts.

Documentation

(1) Minutes of Epilepsy Advisory Committee Meetings.

(2) Secretary's Meeting on Epilepsy, April 12, 1965, DHEW.

(3) Plan for Nationwide Action on Epilepsy, Vols. I-IV. NIH Publication No. 78-276, No. 78-277, No. 78-278, No. 78-279, No. 78-311, No. 78-312, 1978.

(4) Report of the Panel on Convulsive and Neuromuscular Disorders to the National Advisory Neurological and Communicative Disorders and Stroke Council. NIH Publication No. 79-1913, June 1, 1979.

(5) Antiepileptic Drug Development Program of the Epilepsy Branch, NDP, NINCDS. Report prepared for G.H. Glaser, May 1981.

(6) National Research Strategy for Neurological and Communicative Disorders. NIH Publication No. 79-1910, June 1, 1979.

(7) Barkdoll, G.L.: Evaluating the evaluators. Evaluation and the Health Profession 1(3):71-84, 1978.

(8) GOA Report B-202161, July 17, 1981.

DIVISION OF RESEARCH RESOURCES

Director's Overview

The task of determining which research resources are most needed to advance the knowledge-gathering and problem-solving objectives of NIH-supported investigators throughout the academic and nonprofit institutions of our country is an ever continuing challenge in decision-making for the Division of Research Resources (DRR). While currently providing more than 800 resource awards to over 400 research institutions, the Division's five major programs touch upon virtually every scientific discipline and disease area addressed by the over 16,000 research grants funded by NIH. For the most part, too, DRR's nationally distributed resources are located in key institutions where other NIH research grant support is concentrated, thereby linking resource support to grantee institutions holding aggregately more than 80 percent of the total NIH extramural research grant support. Further, by virtue of the varied disease studies conducted in these research resources, DRR has had a very high supportive impact on investigative activities in many important fields of interest at NIH including diabetes, arthritis, nutrition, cystic fibrosis, lupus erythematosis, and Reye's syndrome. In addition to DRR, the NIH Institutes also provide resource support in their areas of concern.

With all the NIH resource programs in perspective, and within its mission, the DRR strategy for the mid-1980s, as presented in its Five-Year Program Plan 1982-86, will be to strive to assemble for the NIH community a more directive course for sustaining and enhancing the continuation of a high level national biomedical research resource enterprise. Whether the parts of the networks of research resources that will be chosen are highly customized or established for multiple uses, they will be required to keep the institution's independent investigations and research teams competitively equipped with the right intellectual and physical tools, environments, and research opportunities to solve scientific problems. With level Federal spending expected in the 1980s in the health research area and continuation of stabilization of funding for research grants, the necessity for improved decision-making, i.e., determining resource needs and values, as well as setting priorities for classes of resources, is evident.

The Division's strategy will entail three key activities. First, DRR will pursue new and intensified measures to bring about a greater awareness of resource capabilities and applications to scientific problems. Second, DRR will explore, experiment with, and establish, as feasible, new ways for economically sharing resources and cooperatively pooling efforts and funding with agencies having mutual resource interests. This effort must also be concerned with the problems of stabilizing research resource support in balance with other parts of NIH extramural support in order to continue to strengthen the research capabilities of grantee institutions. Finally, and most important, the Division will develop improved techniques to identify and characterize the research needs that can and must be met by DRR's research resource programs. This process will have to be adequately shared with the categorical Institutes in order to interrelate broad NIH perspectives for appropriate decisions about research resource allocations and future directions.

The Division's Five-Year Program Plan also identifies three top programmatic priorities. Our highest priorities are:

- Strengthening the program of nationwide shared biotechnology research resource centers.

- Strengthening the Biomedical Research Support Program.

- Retaining the existing base of clinical research resources.

The 1982 budget level will enable the Division to continue to fund all programs at or near 1981 levels, which means the Division will be able to meet nearly all funding commitments made in previous years. The Biomedical Research Support Program will support a new institutional shared instrument program for the procurement of new, and replacement of obsolete, research instrumentation. The Division proposes to fund this by phasing down the Biomedical Research Development Program, in addition to using a portion of funds requested within the Biomedical Research Support Program. Our third priority, the Clinical Research Program, which in fiscal year 1981 supports 71 centers around the country, will continue to provide 80 percent of the NIH extramural inpatient research costs. Research involving outpatients rather than hospitalized patients will be encouraged whenever possible in order to reduce costs to the lowest possible levels.

The 1982 budget will also provide for continuation of other important Division activities. Operation of the seven Regional Primate Research Centers, postdoctoral training of investigators in laboratory animal medicine, and support of resource related projects will be continued at previous levels. For the Minority Biomedical Support (MBS) Program, the 1982 budget will allow for support of 74 of the grants active in FY 1981. Faculty and students will be able to continue their research efforts in a broad range of scientific fields. Based on previous records, the program anticipates that nearly 90 percent of all MBS program graduates will enroll in either graduate or health professional schools.

Looking to 1983, the Division will selectively expand into several program activities. Besides adding several additional communal resources for our two high priority areas, the Clinical and Biotechnology Research Programs, the Division will also invest in further development of biomedical systems models. Another focus will be the expanded development of manpower for communal resources. Funds will be allocated to provide research career development awards for biotechnology and clinical manpower, awards for training of laboratory animal scientists, and special emphasis awards for animal scientists in comparative medicine. Lastly, the Division plans to expand research opportunities for minorities.

FY 1981

Research advances on many fronts have been made during FY 1980 as a result of work done by investigators supported by the Division of Research Resources, or by NIH-supported investigators working at resources funded by the Division of Research Resources. A few of these areas include breast tumor; Reye's syndrome; learning communication skills; vision defects which can be corrected by corneal reshaping; noninvasive techniques developed to monitor blood oxygen; the role of exercise in the management of obesity; maturity-onset diabetes; prevention of heart attacks; immunological therapies for cancer; immunobiology of aging; treatment of physiological impotence in male paraplegics; development of a vaccine against infectious mononucleosis; and research on several tropical diseases, including schistosomiasis, fascioliasis, and others. While this list is by no means exhaustive, it suggests the diversity of research projects affected by DRR activities. In addition to these tangible research results, the Division's programs contribute annually and on a continuing basis to the strengthening of the research environments and systems of hundreds of research institutions including colleges and universities, medical and other health professional schools, hospitals, clinics, and laboratories.

FY 1982 Program Changes

This level will provide for the continuation of all Division programs at essentially 1981 levels, with no major reductions in the number of communal resources supported. Major program changes include the Biomedical Research Support Program.

Under the Biomedical Research Support Program, a new institutional shared instrument grant program will be initiated. These funds will become available in part from phasing down the Biomedical Research Development Program.

FY 1983 Program Changes

For 1983, DRR has no planned new initiatives, major changes in emphasis, cutbacks, or delays in programs. Planned expansions and emphasis of ongoing programmatic activities are as follows:

- Expand research opportunities for minorities.
- Expand development of communal resources including one additional Clinical Research Center and two additional Biotechnology Resources.
- Emphasize Manpower Development for Communal Resources as follows:

--Clinical research manpower including Clinical Associates and off-quarters medical students.

--Research Career Development Awards in Clinical Manpower.

--Biotechnology Research Career Development awards.

--Special emphasis awards for Laboratory Animal Scientists with well-designed research problems in comparative medicine.

--Training of laboratory animal scientists.

- Expand development of biomedical systems models which would serve as a resource to the biomedical research community.

Potential Impact of Program Changes on Three-Year Period

Although the Division has not identified major program changes for 1983-85, the 1983 NIH budget request will provide for some important additional emphasis on development of scientific manpower for communal research resources.

Clearly, clinical research investigators are in short supply and are becoming increasingly scarce. Consequently, the DRR can have a moderate impact by (1) increasing the number of investigators in the Clinical Associate Physician Program from about 40 to 60 (a 50 percent increase), and (2) continuing to encourage support of medical students for a clinical research experience during the summer or an off-quarter in FY 1981. Further, a small number of research career development awards will help add to the pool of clinical investigators.

Another area with some potential impact is that of highly specialized multidisciplinary training for research in biotechnology. This effort will enable scientists to deal with applications of high technology from the physical sciences, engineering, and mathematical and computer sciences to research in biological systems, and research data handling and analysis. Scientists with these skills are in short supply and much sought after.

Another gap in manpower for communal resources is in the area of comparative medicine for laboratory animal scientists. There is a need to identify new animal models, to examine various types of animals for suitability for both categorical and disciplinary areas of biomedical research, to characterize them, and to provide opportunities for comparative studies of biological processes. DRR, by offering a number of research career development awards in comparative medicine, could provide some of the key animal scientists adequately trained to meet these various research requirements.

DRR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Acting Director
Division of Research Resources

DATE: January 14, 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Division's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

I would like to take this opportunity to commend you and your staff for the progress that has been made in the Division's planning function in the past two years. This has helped all of us to understand better the significance of DRR programs to the NIH community and is essential to our efforts to collectively consider future directions. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

FY 1981, Planning Assumption

$178 million will be required to support DRR's commitment base activities; $5 million will be allocated to the Biotechnology Resources Program and $1 million to support the Minority High School Summer Student Research Apprenticeship Program.

FY 1982, Planning Assumption

This level would provide for continuation of all Division programs at essentially 1981 levels, with no major reductions in the number of resources supported, and no major program changes except for the Biomedical Research Support Program.

Under the Biomedical Research Support (BRS) Program, a new institutional shared instrument grant program is proposed at $3.8 million. These funds will become available in part from phasing down the Biomedical Research Development Program. If the proposed initiative is not approved, these funds will be included in the pool for allocation via the BRS grants.

FY 1983

Current Level

- At this level no new awards would be made, and some awards in each program would terminate or phase out due to the impact of inflation, Some specific effects would be the phaseout of a number of general clinical research centers, severe reductions in the Primate Centers Program, termination of several biotechnology resources, suspension of CLINFO (Clinical Data Management and Analysis System) diffusion, and reduction in research projects at minority biomedical support (MBS) institutions.

Current Services Level

- This level would permit the operation of all Division programs at essentially the 1982 level of activity, with no new awards and some added emphasis on providing clinical research opportunities for medical students.

Intermediate Level

- Under this level, all Division programs would not grow equally, ranging from 0.2 percent of the program growth for the Animal Resources Program to 8.0 percent for the General Clinical Research Center (GCRC) Program. Emphasis would be placed on the General Clinical Research Center Program to strengthen existing facilities and provide additional training opportunities, on the Biotechnology Program to develop new national resources and establish training opportunities, on the Biomedical Research Support Program to increase purchasing power with further development of the new shared instrumentation grant program, and on the Animal Resources and Minority Biomedical Research Programs to establish research training or student experiences in research.

Request Level

- This request reflects the direction, priorities, and dollar levels stated in the Division's Five-Year Program Plan, 1982-86.

- Increases would be used primarily for major institutional renewal activities in every program area, expansion of the institutional shared instrument program, increases in training activities in the Animal Resources, General Clinical Research Center, Minority Biomedical Support, and Biotechnology Resources Programs.

Impact of Stabilization

If the stabilization initiative results in reduction of center and resource support by the Institutes, this could lead to increased demands on the Biomedical Research Support Program, additional pressure for pilot research projects, the use of shared instruments, increased requests for alterations and renovations, and increased demand for the shared use of animal resources.

Mechanisms for Institutional Renewal

Research environments within academic institutions are in need of restoration as are the research resources in these settings.

To assist in dealing with these problems, the following actions should occur:

- Increasing the funding level of the Biomedical Research Support Program. The current funding is about 2 percent of the total NIH research grant level. The plan is to increase it by two-tenths of one percent each year to achieve a 3.1 percent level by 1986.

- Further development of the shared instrument grant program.

- Sustaining initiatives in the Biotechnology Resources Program. Support in this program is about evenly balanced between computer resource activities, information and knowledge systems, and instrumentation for the study of biological structure and function.

- Upgrading and carrying out necessary renovations in the primate centers, general clinical research centers, and minority biomedical institutions, and initiation of a major construction effort for institutional laboratory animal facilities. Needs for the latter are discussed in the National Survey of Laboratory Animal Facilities and Resources; $10 million would meet about 1 percent of the estimated need here.

Resource Manpower Development

Proposals here involve expansion of existing activities and development of selected initiatives. The former includes research training for veterinarians in shortage areas in laboratory animal medicine and expansion of the Clinical Associate Physician Program, including expansion of research opportunities for medical students off-quarters (three months training, $100,000 to initiate, additional $200,000 by 1983, three students per GCRC supported). New initiatives include development of a Minority Faculty New Investigator Research Award to develop young investigators' careers--the support of minority students to become involved in research at majority institutions, and targeted predoctoral fellowships to minority graduate students at campuses of their choice, and biotechnology oriented fellowships in such areas as computer sciences, biomathematics, bioengineering, and physical chemistry to strengthen the interface with biologists and to enhance links to industry. The proposed initiatives involving minority investigators need to be discussed and coordinated with the plans and ongoing efforts of the other Bureau/Institute/Divisions (B/I/Ds).

Action Items

- Please submit a two- or three-page report on the impact of stabilizing NIH research project grants on the Division's programs. To the extent possible, please describe those uses of the Biomedical Research Support Grant for which you would expect to see greater demands.
- Please submit a short report outlining, in the Division's Biotechnology Resources Program, any existing relationships this program has with private industry, and any that might reasonably be planned in the future.
- Please submit a table which displays separately, in constant dollars, since 1969, maintenance and research costs in the Primate Centers Program.
- Please submit a list of all regional biotechnology resources, with a display of those BID-supported projects that use them. Include a description of the service charge policy, if any, that obtains for each resource and a summary of the revenues derived from user fees over the last two years.

Institutional Revitalization

Statement of Issue

Need to bolster resource mechanisms for institutional revitalization.

Discussion of Issue

Varying degrees of erosion, deterioration, and obsolescence of research facilities and instrumentation exist within the many academic research institutions where NIH extramural grants are concentrated. These essential research environments are in need of restoration, as are some of the research resources placed in the institutions to provide high-quality biomedical research settings in which research problems can be solved. Bolstering these resource mechanisms will contribute importantly to revitalizing the institutions. Specifically, the following matters are of concern:

- The Biomedical Research Support Program's funding levels should be increased to reach goals in DRR's Five-Year Program Plan.
- An institutional shared instrument grant program available to grantees of all NIH Institutes would address the equipment availability and accountability requirements.
- Initiatives in biotechnology resources should be sustained to assure development of state-of-the-art techniques applicable to scientific problems in biological and medical sciences at institutions.
- Upgrading and carrying out necessary renovations in:

  --DRR-supported resources: Primate Centers, GCRCs, and MBS Institutions.

  --Institutional laboratory animal facility construction (as per the Five-Year Program Plan).

- Data management/statistical capabilities for clinical research (CLINFO) should be provided to optimize the timely assembly and analysis of research data.

Manpower Development

Statement of Issue

Need for resource manpower development.

Discussion of Issue

DRR provides excellent sites for developing research skills and careers in many fields and disciplines, particularly areas related to research resource technologies and functions. Expansion of existing programmatic activities, and selected new initiatives in the manpower area, are warranted for DRR in the light of various social, scientific, and economic circumstances characterizing the health research enterprise. These are summarized as follows:

Initiatives

- Minority Faculty New Investigator Awards to develop young investigators' careers.
- Support of minority students' involvement in research at majority institutions is another key way to develop potential minority biomedical research scientists, particularly in high-quality research laboratories already supported by NIH.
- Targeted predoctoral fellowships to minority graduate students at campuses of their choice to help divert to research careers the more than 50 percent of MBS and MARC (minority access to research careers) students who choose other health careers upon matriculation.
- Biotechnology-oriented fellowships to develop the skills needed to interface the physical sciences with the biological problem areas and applications (mathematicians, bioengineers, physical chemists.)

Expansion of Ongoing Programs

- Development of laboratory animal veterinary scientists for post-professional education in projected shortage areas of comparative laboratory animal medicine and pathology.
- In the face of the decline in clinical research support, with the concomitant dissociation of young physicians and research careers, it is particularly timely to expand activities like the CAP (clinical associate physician) program to enable more talented young M.D.'s to gain sufficient research experience to develop independent careers in clinical investigations. As of 1979, 90 percent of CAP graduates had attained full-time faculty status and one-half had NIH grant or contract support.

PROGRAM PERFORMANCE SUMMARY

MINORITY BIOMEDICAL SUPPORT PROGRAM

Program Description

Problems Being Addressed

The Minority Biomedical Support (MBS) Program was established in response to recognition of the severe underrepresentation of minority individuals in biomedical sciences. For example, of some 77,000 Ph.D.'s in the natural sciences in 1970, only about 1 percent (800-1,000) were blacks, Hispanics, or American Indians.(1,2,3) Asians comprised about 4 percent and were not underrepresented in proportion to the total Asian population as compared to the other minorities.(2) Even today, although ethnic minority groups comprise more than 18 percent of this country's total population, they make up less than 2 percent of the Ph.D. science and engineering workforce.(4)

Historically, minority institutions have produced most of the minority undergraduates who subsequently obtained the Ph.D. degree in biomedical and other sciences. However, the limited biomedical research thrusts at these institutions have not inspired enough of these students to choose biomedical research careers. The paucity of biomedical research at minority institutions can be attributed to lack of funds, inadequate facilities and equipment for research, and institutional emphasis on teaching as the predominant mission.

Legislative History

To assist in correcting these deficiencies, in fiscal year 1972, under the authority of Section 301(c)--now 301(a)(3)--of the Public Health Service Act, as amended (42 U.S.C. 241(d)), the Division of Research Resources (DRR) initiated the Minority Schools Biomedical Support Program. Later renamed the Minority Biomedical Support (MBS) Program, it was designed to relieve the shortage of ethnic minorities engaged in biomedical science research by strengthening institutional research and student research participation at colleges, universities, and health professional schools, where 50 percent or more of the students are classified as minority, and other institutions that have demonstrated special commitment and assistance to ethnic minority faculty and students. The program was expanded in 1975 to include two-year institutions.

The program is consistent with the mandate expressed by President Nixon in his message to Congress proposing measures to "Expand Opportunities for Higher Education" (February 22, 1971)--in which he called for assistance of government at all levels to help black institutions that are "faced with a historic inadequacy of resources." It is also consistent with Executive Order 12232 on historically black colleges and universities as signed by President Carter on August 8, 1980.(5)

On September 15, 1981, President Reagan signed Executive Order 12320 and said, "I'm very happy to sign this Executive Order which commits the Federal Government to more support with regard to our historic black colleges, and also it commits us to a program of encouraging more private support with those same educational institutions."(6)

Funding and Staffing

Table 1

Dollars in Thousands

	FY 1978 actual	FY 1979 actual	FY 1980 actual	FY 1981 estimate	FY 1982 estimate
Appropriation levels	$10,758	$14,584	$18,089	$18,857	$18,818
No. of grantees	71	73	80	84	74
No. of subprojects	399	405	493	500	480
Co-funding or intra-agency	$ 3,487	$ 4,596	$ 6,036	$ 6,480	$ 5,702
No. of Institutes	6	10	10	10	10
No. of subprojects	86	117	145	158	139

The staff consists of eight part- and full-time (PFT) employees: a program director (HSA), three Health Scientist Administrators; one grants technical assistant, and three secretaries. Although program branch responsibilities require considerable staff time for the management of grants, planning, and evaluation, a substantial amount of staff time is required in the review of applications. These latter responsibilities tend to put heavy burdens on the staff and detract from the needs in the program management of grants that involve a complexity of institutional environments where biomedical research is in its infancy.

There has also been an increasing workload in the activities involving co-funding and intra-agency agreements as indicated in the above table.

Program Objectives and Activities

Program and Management Objectives

The overall objective of the MBS Program is to increase the number of ethnic minority biomedical research scientists. This is accomplished through three interrelated thrusts. They are:

- Strengthening of the capability of eligible institutions to support the conduct of quality research in the health sciences.

- Support of faculty at eligible institutions as they initiate or expand their biomedical research interests and capabilities.

- Support of minority students on research projects at the undergraduate and graduate levels in order to motivate and prepare them for careers in biomedical research.

The terms in which achievements of these objectives can be assessed include monitoring:

- The number of scientists at these institutions who are engaged in biomedical research;

- The development of facilities and resources used to support biomedical research (i.e., laboratories, equipment, animal quarters, etc.) at these institutions;

- The scientific productivity of investigators in terms of numbers and kinds of papers presented and published;

- The expanding base of biomedical research at these institutions in terms of submittal, approval, and funding rates to/from traditional funding sources;

- The rate of increase in undergraduate and graduate participation in biomedical research projects at supported institutions;

- MBS student/participants rate of entry into and completion of graduate and professional schools; and

- The rate of selection and pursuit of research careers by students following MBS participation.

Current Program Activity

The MBS Program offers diverse opportunities for minority students and faculty to become actively exposed to, and involved in, biomedical research while developing institutional capability. This involves activities in three areas:

Institutional Development:

- Acquisition of modern, sophisticated scientific equipment;

- Renovation and upgrading of research laboratories, animal care facilities, etc.;

- Improvement of grants management and other managerial skills;

- Expansion of faculty (and the expertise base) in the biomedical sciences as substitutes are hired to replace released time faculty. The result is usually an improved curriculum with new or updated science courses and upper division courses designed to benefit from the research equipment availability;

- Increased numbers of research-oriented faculty capable of obtaining increased numbers of grants and contracts.

Faculty Involvement and Development:

- Academic-year release time allows research participation rather than 100 percent teaching activities;

- Summer salary support allows a continuity of research effort by faculty who would normally teach or seek employment at some research site which is removed from his/her home;

- Research develoment by faculty leads to an ability to teach at the cutting edge of science;

- Funds are provided to travel to scientific meetings, bring in experts as consultants, and to help defray publication costs;

- Where needed, funds are provided to allow faculty to take short research courses, participate in workshops, and obtain research expertise in a variety of ways;

- Funds are provided for needed technical support to carry out the research.

Student Involvement and Development:

- Students participate directly in research activities and thereby gain skills needed for future career success;

- Seminars, symposia and scientific meetings are attended where students are able to share their research results through formal presentations or informal discussions;

- Students become co-authors of scientific publications as a culmination of the scientific learning process;

- Students receive partial compensation (salary, wage) for their research activities.

Evidence of Program Performance

Information Used to Assess Program Performance

The kinds of information and activities being used to monitor program performance include:

- Annual grantee progress reports;
- Grants funding data;
- Published papers and abstracts of scientific meetings, workshops, and symposia;
- Staff visits by program managers;
- On-site visits by teams of scientific experts during the review of applications;
- Priority scores assigned to various applications by the General Research Support Review Committee;
- Data on Council actions;
- Advent of co-funding by other agencies.

Evidence of Program Effectiveness Relating Directly to the Stated Objective of the Program

Approximately 4,000 minority students have participated in the program since 1972. Nearly 3,500 students have graduated with the bachelor of science degree from participating institutions. Approximately 75 percent of these students have gone on to advanced study in biomedical science areas (from Annual Progress Reports):

- About 900 have elected to attend graduate schools.
- About 1,600 have entered professional schools. It is assumed that a good number of these will become clinical investigators because of their MBS-supported experience. In 1980, eight percent of those going on to medical school were pursuing a joint M.D./Ph.D. program.
- The students who did not pursue advanced studies are employed largely in jobs related to health.

At ten MBS-eligible institutions, approximately 50 minority students received Ph.D. degrees while participating in MBS-funded projects. They are currently engaged in biomedical research, either at the postdoctoral or faculty level.(7)

Specific examples of student involvement and participation follow:

Howard University--The MBS Program has supported 268 students at Howard University during the period 1972-79. The student participants include: 122 graduates, 109 graduate students, 24 dental students, and 13 medical students. A total of 80 have completed their undergraduate degrees at Howard University: 14 completed the Ph.D., 21 completed the M.D., 27 completed the D.D.S., 15 are presently in Graduate School pursuing a Ph.D., 34 are presently in medical school pursuing an M.D., 1 is in veterinary school, 2 are in dental school, 88 did not pursue advanced degrees in biomedical sciences but hold jobs as teachers, technicians, etc. The other 67 students are still participating in the MBS Program.

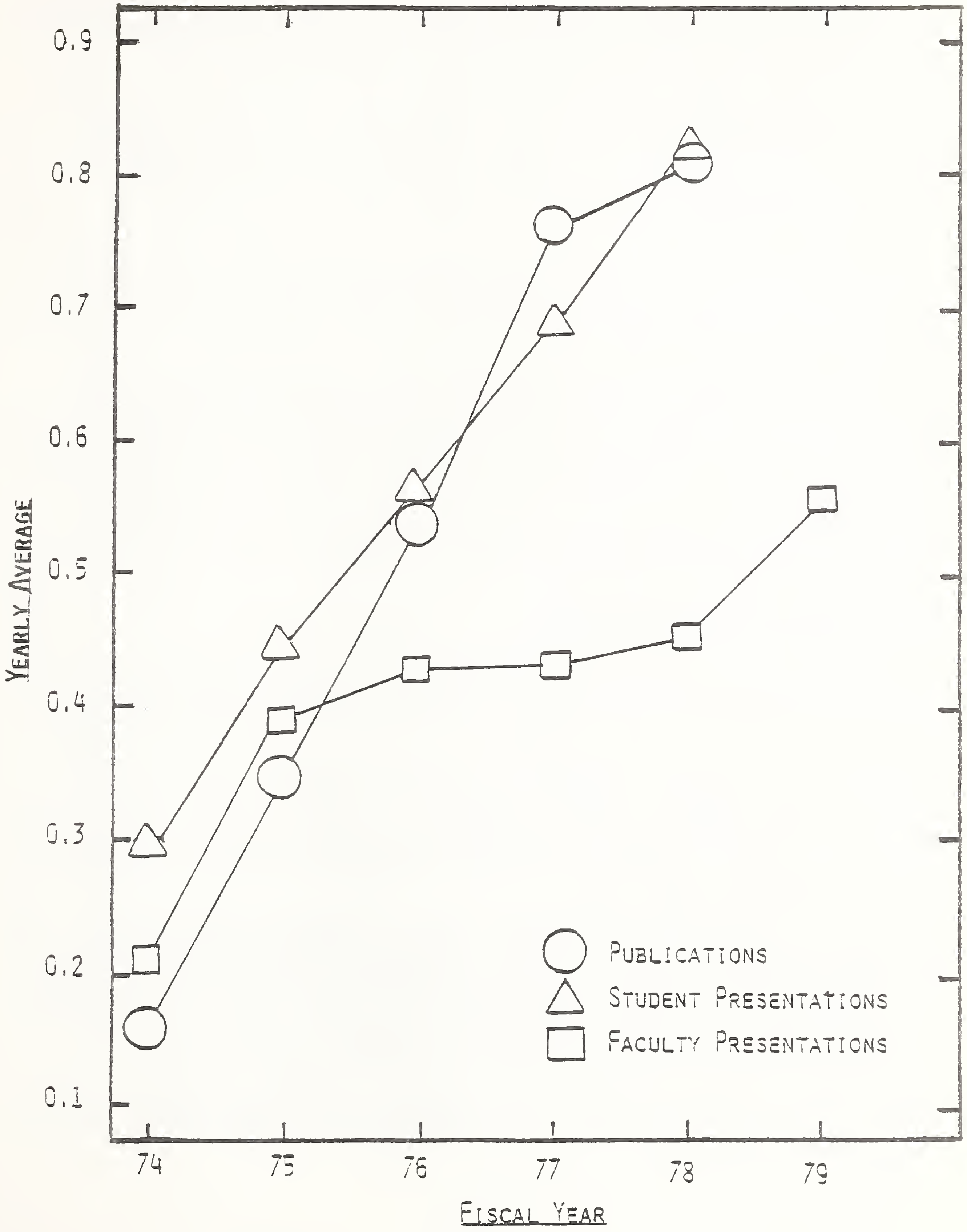
University of New Mexico--During the first five years of the MBS Program (1973-78), over 210 students have participated and 101 have been awarded degrees at U. of New Mexico, including 19 master's, 5 Ph.D's, and 3 M.D.'s. Twenty-two of the students receiving bachelor's degrees are currently enrolled in medical schools and 12 in graduate schools. Twenty have gone to work in health-related fields.

Meharry Medical College--Only graduate students are supported through the MBS Program at Meharry. There have been 12 students graduated with a Ph.D. to date. One of them has elected to go for the M.D. degree, and the other 11 are in biomedical research careers. There are presently 17 graduate students supported by the MBS Program at Meharry, and all are pursuing the Ph.D. degree.

University of Puerto Rico, Rio Piedras--More than 200 students have participated in the SUBE-MBS Program since it began in 1973. The faculty participants during the current budget period (09 year) have collectively been involved with 199 students, of whom 76 have obtained the B.S., 22 the M.S., and 3 the Ph.D. from the University of Puerto Rico. A number of these graduates have entered medical, dental, and graduate schools. Others are currently employed as teachers and researchers in facilities which are located primarily on the island of Puerto Rico.

There are currently 1,500 students and 600 faculty engaged in about 500 distinct research projects supported through the MBS Program. Many investigators have effectively changed fields in order to carry out biomedical research. The productivity of the faculty and students as measured by publications and research papers presented at scientific meetings has increased in the following manner. In 1974 only 15 percent of the faculty published at least one paper. This increased to 34 percent in 1975, 53 percent in 1976, and 81 percent by 1978. Similarly, faculty presentations increased from 29 percent in 1974 to 82 percent in 1978. Student presentation of research papers increased from 20 percent in 1974 to 55 percent in 1979. There is a fivefold increase in research productivity by faculty and almost a threefold increase for students. These changes are depicted graphically on the following page.(7)

PRODUCTIVITY - MBS PROGRAM - 1974 - 1979



As a further expansion of its impact, the MBS Program established an administrative mechanism in FY 1975 for involvement of other Institutes of NIH in funding certain targeted research projects occurring in MBS-supported institutions. The majority of the NIH Institutes and the National Institute of Mental Health (NIHM) are presently engaged in these agreements with the MBS Program. Such arrangements permit the cooperating Institute to pay the costs for projects that are of direct concern to their stated missions. The MBS Program provides for the overall review and management of these projects, including budget negotiations and monitoring progress and accomplishments. (See Table 1 below.)

As part of the Program goals to develop faculty and institutional capabilities in biomedical research efforts, the Branch planned and sponsored four grantsmanship workshops during FY 1980. Technical assistance in preparing high-quality research grant applications was provided to faculty from minority institutions. Staff members from MBS and other elements of the NIH were utilized. The workshops were developed along the lines of a minicourse and included illustrated lectures, which were followed by small work group sessions. Selected research grant applications were discussed and hands-on experience in critiquing each portion of the applications was provided. In addition, a budget was developed for a mock application. A total of about 310 faculty members from MBS grantee institutions participated in the four workshops. Participation was limited to those faculty who had little or no experience in writing research grant proposals. At least one grants officer from each institution was also invited.

Other Evidence of Program Efficiency, Effectiveness, and Responsiveness

The quality of science at MBS-supported institutions and the reputations of MBS investigators have continued to increase. When the program started, the projects were very general in nature and were restricted to basic biological studies. The currently supported projects are very specific and sophisticated studies at the cutting edge of biomedical research, such as recombinant DNA, vaccine development, clinical studies, and development of new drugs. There has been a marked change in the nature of projects from very general to the specific and sophisticated areas supported by the Institutes of NIH and the Alcohol, Drug Abuse, and Mental Health Administration. Examples of MBS research efforts are the following:

An investigator in the Department of Natural Sciences at Medgar Evers College and collaborators at the Albert Einstein College of Medicine have been the first to demonstrate that there are drug binding sites in the pedal ganglia of the marine mollusc *Mytillus edulis*. The nervous system of this invertebrate is considerably less complicated than mammalian systems but is a good model for monitoring cellular and electrical changes induced by drugs. The investigator chaired a session and reported on his research at the XXVIII International Congress of Physiological Sciences in Budapest, Hungary, in July 1980. He plans to present new research findings at the International Congress on Comparative Neuropharmacology to be held in Japan in 1981.

Investigators at Bishop College, an undergraduate institution in Dallas, have developed a rapid (four minute) procedure using ^{125}I to qualitatively and quantitatively determine the molecular weight of RNA samples. This rapid iodination procedure, when combined with two-dimensional gel electrophoresis, simplifies identification of RNA without interference from impurities.

At Howard University, an investigator is carrying out research on breast tumor growth. By studying mammary cancer induced in laboratory rats by a carcinogenic agent, he is beginning to delineate the role of hormones and certain hormone inhibitors on the rate of tumor growth. Approximately 40 percent of the mammary carcinoma occurring in American women appears to be hormone dependent. Recently it was demonstrated in this laboratory that the compound CI-628, a female hormone antagonist, which competively binds to hormone receptors, induces tumor regression, and terminates the synthesis of an important catalyst in tumor cells. It was also shown that another female hormone antagonist, progesterone, results in a blockage of the biological processes involved in tumor development.

Anti-inflammatory steroids are being developed by researchers in the College of Pharmacy at Florida A&M University in Tallahassee.(8) Studies in rats indicate that two new compounds have a marked local anti-inflammatory action without any of the usual toxic effects caused by the corticosteroids currently employed for topical application.

Biologists at the University of Puerto Rico, Rio Piedras campus, are developing a vaccine against schistosomiasis, a parasitic disease which affects 10 to 15 percent of Puerto Ricans and over 200 million people in tropical areas throughout the world.(9) Tests of a new vaccine, isolated from a related parasite, Fasciola hepatica, which infects the livers of cattle and sheep, gave a significantly higher degree of protection than has been obtained using other methods. Efforts are continuing to improve the vaccine to achieve at least 80 percent protection consistently, to identify all the protective antigens and optimize treatment regimens and, eventually, to test the vaccine in non-human primates.

MBS investigators at the University of Maryland, Eastern Shore, have been studying marine algae in order to isolate medically active compounds (bioactive compounds from natural sources include digitalis, reserpine, atropine, and colchicine). They are studying a species of marine "red-tide" dinoflagellates which produce some of the most potent toxins known to man. The study of the toxins is important not only for the potential of obtaining new compounds for the treatment of disease, but also for the development of an effective treatment for human or animal intoxication from venoms of toxic marine organisms. The team has been successful in culturing large volumes of cells under conditions which promote high toxin production, and has improved techniques for harvesting and purifying the toxic material so that physiological, pharmacological, and toxicological studies can be carried out.

Ongoing Assessment of Program Performance

None.

Proposed Studies That Will Assess Program Performance

A proposal to let a contract for a short-term evaluation of the MBS Program in FY 1982 has been conditionally approved by DHHS. Specifically, the contractor will: (a) review and revise as appropriate the work already done by program staff in describing the program, setting out objectives, specifying performance indicators, identifying major program problems and issues, and characterizing evidence already collected regarding program process and performance, (b) develop measures of progress and success in achieving the objectives and specify processes of data collecting and reporting--including new or modified annual reports and/or program data systems--that will enable the program to monitor progress and success, (c) perform a short-term evaluation of process, progress, and success using data that are readily available and/or easily obtainable, and (d) characterize long-term/full-scale evaluations of the program that could be undertaken, specifying the information that would result, the probable cost and duration, and the likelihood of success and utility.

Major Issues or Problems Cited by Organizations

In testimony presented before the House Appropriations Subcommittee on Labor, Health, Education and Welfare on June 16, 1981, representatives of the National Organization of Black Chemists and Chemical Engineers and the Organization of Black Scientists identified the need for "Comprehensive Centers of Graduate Research in Biomedical Science" at selected minority institutions. The centers would serve to increase the number of minorities receiving the Ph.D. in biomedical sciences by considerably upgrading the ability of a few minority institutions to contribute more fully in this endeavor.

A study and report of the Women's College Coalition advised DRR of the need to develop a program similar to the MBS Program for women's colleges. (10)

Other Major Barriers and Issues Relating to Program Performance

The program has identified a number of barriers, the removal of which is seen as critical to improve program performance. Based on program judgment, taking into account the advice of the MBS Program Advisory Subcommittee of the National Advisory Research Resources Council, those listed below are judged to be the most important:

- A number of investigators who are participating in the MBS Program are at a stage where their research careers need to be enhanced by more intensive research pursuit over an extended period. The Research Career Development Award (RCDA) is already in existence at NIH and thought to be the best mechanism for accomplishing this aim. An RCDA provides salary for an investigator for a five-year period and requires that he/she spend a minimum of 90 percent effort in research.

- Many MBS-supported institutions are in small and sometimes isolated settings. In addition, the breadth of research at these institutions is usually limited. To correct this deficient environment for the MBS students at these institutons by exposing them to more intense research atmosphere and by allowing them to establish possible contacts for graduate work, summer research experiences are proposed. Salaries, as well as travel support, would be provided for students to spend a summer at a mainstream laboratory in a major research setting. A possible variation would be to extend this type of support into the academic year.

- A large percentage of MBS students go on to study in professional schools. In order to assure that more MBS participants continue in biomedical research, it is proposed to allow those MBS graduates who attend professional schools to engage in research during the summer with a mentor on the professional schools' faculty. This would serve to increase the number of research clinicians.

- The amount of support for graduate education appears to be decreasing nationally which means that fewer slots for graduate study will be available. Predoctoral fellowships are needed to enable minority students graduating with B.S. and M.S. degrees to continue study toward Ph.D. degrees in biomedical sciences at any institution where an appropriate opening can be found. The program's previous investments in the MBS student participants can be preserved through this mechanism.

- There is a pressing need for major instrumentation at MBS institutions. Worn out and obsolete equipment needs to be replaced and MBS investigators need sophisticated equipment which would make them competitive with their counterparts at other institutions. Awards would be limited to those grantee institutions where a critical mass of productive investigators could have access to the resource.

Documentation

1. Minority Biomedical Support: A Powerful Program for Change in Predominantly Minority Colleges and Universities Presented at AAAS Meeting, February 27, 1974. Author--Dr. Benjamin H. Alexander, et al.

2. Doctorates in Science and Engineering (NSF Publication NSB 73-1), 1973.

3. Negroes in Science: National Science Graduates, 1876-1969, Author--James Jay, 1971

4. Women and Minority Ph.D.'s in the 1970's: A Data Book. The National Research Council, Commission on Human Resources, 1977.

5. Federal Register, Volume 45, No. 157, pp. 53437-53438

6. Presidential Documents, September 15, 1981, pg. 980.

7. FY 1980 MBS Annual Report, Division of Research Resources, National Institutes of Health

8. Research Resources Reporter, Volume 5, No. 10, pg. 13

9. Research Resources Reporter, Volume 4, No. 8, pp. 1-4

10. Report Submitted to Division of Research Resources, National Institutes of Health by Womens College Coalition Workgroup, Women in Biomedical Research, A Statement of National Need, July 20, 1979.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

Director's Overview

The John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) will be reviewing its programs over the next few months to determine their effectiveness in contributing to the overall health research goals of NIH. Although, unlike other Bureau/Institute/Divisions (BIDs), the FIC does not directly support research projects, it has an important impact on the national health scene because it fosters interrelationships with foreign scientists. This brings to the United States a knowledge of diseases not readily studied in this country and of technologies developed and tested elsewhere in the world. At the same time, both U.S. and foreign scientists are profiting from the mutual stimulation of collaborations here and abroad. We already have substantial evidence that our International Research Fellowship Program is effective,based on a recent in-depth evaluation of that program. Further,anecdotal evidence suggests that many former International Research Fellows are now in positions of leadership and are nominating their junior colleagues for participation in the program.

We must, however, subject our other programs to the same critical review. To that end we plan to review the bilateral exchange programs to determine whether the NIH and the Department are benefiting from the many bilateral agreements already in place and what program changes are possible to improve the content and equity of the scientific exchange. We have established a forum for these discussions through regular convocation of the BID international representatives. We will draw upon the various experiences of the BIDs with selected bilateral exchanges to develop a realistic understanding of the nature of the exchanges, the benefits realized, those factors that inhibit success, and the prospects for future successes. We will use this knowledge in renegotiation of existing agreements with health ministries,and in initial negotiations in the future, to improve the content and the product of these bilateral activities.

The Fogarty International Center is aware of the importance of relating the work performed by foreign nationals to the U.S. scientific enterprise. We are developing a program planning capability within FIC to evaluate the foreign scientific enterprise we support and relate it to domestic health problems and associated biomedical research activities. We will use this ongoing assessment to improve our funding decisions in the International Research Fellowship Program.

We intend to establish an advisory mechanism to assist us in these endeavors. We will establish a permanent Council or Board to help us with our program reviews as well as to provide advice to the FIC on international health priorities.

The Task Force To Assess the Mission and Functions of the Fogarty International Center made a strong recommendation that FIC utilize the unique resource of our most visible program, the Scholars-in-Residence Program, to identify and study health research issues of international importance. We will have the first real opportunity to implement this recommendation in FY 1983, since present scholars and those invited for FY 1982 were not nominated with this objective in mind. We will attempt to fulfill the task force recommendation by seeking nominations for FY 1983 of individuals who can make significant contributions to the International Issues Study Program.

FY 1981 Program Accomplishments

The Fogarty International Center continued its efforts in FY 1981 to sponsor activities dealing with the worldwide eradication of several important diseases. A conference on this topic was led by a Fogarty Scholar, Sir Charles Stuart-Harris, and the proceedings will be published this fall in the scientific literature. The Center, assisted by leading scientists, is continuing its activities in this area and has planned a series of meetings to evaluate separately the feasibility for area or worldwide eradication of measles, poliomyelitis, and yaws. The World Health Organization and the Pan-American Health Organization, as well as U.S. Federal agencies, are collaborating with the Fogarty International Center in this endeavor.

As part of its ongoing efforts to match the scientific capabilities and program needs of the BIDs with sources of funds, the FIC established a relationship with the U.S. Agency for International Development (AID), which may lead to the funding of projects aimed at creating scientific capacity in developing countries in the future. The BIDs' response to the FIC initiative was gratifying, with over 35 projects being proposed for consideration by AID. While it is not certain how many of these projects will make it to the final round of consideration, FIC intends to work closely with AID on this and subsequent rounds of proposals to take advantage of this opportunity.

In FY 1981, staff of the FIC made the first attempt at a comprehensive overview of all NIH international and related activities. The BID response to this effort suggests that it has been worthwhile and should be continued, probably on an annual basis. The FIC proposes to continue this effort, refining and expanding it as seems appropriate, based on the needs of the BIDs, the FIC, and OD/NIH.

FY 1982 Program Changes

The resources available to the Fogarty International Center in FY 1982 will force a continuing evaluation of our funding priorities, since the anticipated level in real dollars is less than that provided for in FY 1981. Some programs will be maintained at current levels, while others will be curtailed to make a balanced program possible.

Program Changes

We will divert funds from the Senior International Fellowship Program and, if necessary, the International Research Fellowship Program in order to maintain the Scholars-in-Residence Program at the present level. The Senior International Fellowship Program will bear the greater portion of the reduction in order to maintain the International Research Fellowship Program at an acceptable level that will not compromise this program, which provides opportunities not otherwise available to promising scientists in many countries.

The FIC will realize the full impact of discontinuing our management of extramural and non-FIC-initiated intramural conferences, and we will allocate the savings that accrue to the fellowship programs and to support R-13 conference grant applications.

New Initiatives

- FIC will negotiate a training program for scientists from developing countries in certain health specialties, utilizing funds from the Agency for International Development.

- FIC will work with the Division of Research Services, using AID funds, to establish a center for the training of biomedical instrumentation repair specialists from developing countries.

- FIC will develop a small trial program of grants, utilizing AID money, to assist scientists from developing countries to continue their research on return to their home countries.

- FIC will assist the People's Republic of China to organize a nominating committee to screen applications for our International Research Fellowship Program.

- FIC will sponsor a workshop to address the question of how best to correlate the results of epidemiology studies with the development of health policies. This workshop will provide preliminary information upon which to base an International Issues Study that could involve the Fogarty Scholars, the Office of Medical Applications of Research, and other NIH and HHS components.

- The FIC will begin discussions with the Agency for International Development and the Gorgas Memorial Institute in an attempt to develop the Gorgas Memorial Laboratory into a tropical disease research center for all of Latin America. This laboratory would function in the same manner as INCAP* and would be funded by contributions from PAHO** member states. A similar proposal is under consideration to convert the CDC-NIH Lassa Fever Studies Laboratory in Sierra Leone into a regional reference, research, and training laboratory for the countries of West Africa.

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* Institute of Nutrition of Central America and Panama.
** Pan American Health Organization.

FY 1983 Program Changes

Change in Program Emphasis

One of the main questions which the FIC will be considering during FY 1983 is whether, and in what ways, the capabilities of the BIDs and of the American biomedical research community can aid the less-developed countries (LDC) to realize their health goals, while at the same time assisting in the general advance of biomedical knowledge to the benefit of the American people. This is a particular conundrum in view of the fact that--on the surface at least--there is a considerable mismatch between the highly advanced and specialized interests and skills of the American biomedical research community, and the often very basic health-related needs of the LDCs. It can be (and has been) argued that rather than a service, the NIH does a disservice to developing countries by training their scientists in the latest techniques and technology of biomedical research. Even if these scientists choose to return to their home countries, and even if they are able to find funding for continuing their research, the products of this research (and therefore the funds and talents which produce them) are seldom of direct benefit to the most critical health problems of those countries. There may be only a few areas, such as certain tropical diseases, where there is a good match between the needs of LDCs and NIH capabilities. This being the case, the exploration of appropriate scientific relations with developing countries, followed by the definition of an action plan, will be a major effort during FY 1983.

New and Ongoing Initiatives

- If the results of our evaluation of the benefits that accrue to LDCs as a result of participation in our International Research Fellows (IRF) Program are positive, the FIC will initiate a small-grant program to provide "seed money" to returning IRFs. These funds will aid them to begin independent research activities. These funds will also partially reduce the drain on the already overburdened health budgets of the LDCs and speed the returning fellows' entry into productive research on important disease problems.

- The FIC will continue its efforts to interact with the Agency for International Development, the World Bank, and other organizations to promote NIH objectives and obtain funding assistance for programs that are of mutual interest.

- The FIC will have additional opportunities in FY 1983 to appoint Scholars-in-Residence who are interested in the International Issues Study Program and who could contribute their interests and expertise to further the objectives of this program.

- The FIC will seek to expand the IRF Program by stimulating the development of new national nominating committees in selected countries. Possible countries to be added to the International Research Fellowship Program are the People's Republic of China, Hungary, and Romania.

FIC

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
Fogarty International Center

DATE: MAR 3 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Institute's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

It was a pleasure to meet with you in your new capacity as Director, FIC. I look forward to working with you in developing further the role and investment strategy of the NIH in international health activities. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

Since the report in 1979 of the "Task Force To Assess the Mission and Functions of the Fogarty International Center," the FIC, under interim leadership, has progressed steadily in implementing recommendations for strengthening its role as the focal point for NIH activities related to the international aspects of biomedical and behavioral research. Now, under the guidance of the new permanent Director, efforts will be continued to implement the recommendations and to plan and implement additional program initiatives.

Impact of Stabilization

The FIC does not support research grants, except for the core grant to the Gorgas Memorial Institute and, consequently, is not directly affected by the stabilization initiative. However, in view of the need to mount new programs in the face of constricted budgets, the FIC has developed a strategy for reallocation of funds among competing programs.

Priorities Among Current Programs

- The highest priority is accorded to the Scholars-in-Residence Program, which enables the NIH to attract outstanding scientists to the campus to participate in the programs and activities of the Institutes and to collaborate with other scholars throughout the scientific community. Funds will be provided to maintain the current level of 10 scholars, which is considered necessary to sustain a critical mass for fruitful interaction and exchange of ideas. The FIC will continue to develop and refine the policies and procedures governing the length of appointments, the number of visits permitted by an individual scholar, the selection process, and other aspects of the program.

- The next level of priority is represented by the International Research Fellowship Program, which provides fellowships to foreign scientists to pursue studies in laboratories in the United States. The number of fellows supported in 1981 and 1982 will decline from the 1980 level. These adjusted levels will permit funding of approximately 60 to 70 new awards each year. Since candidates are provided by nominating committees in 46 countries, it is quite possible that some of the countries that participate will not have a single fellowship awarded to a nominee from that country.

- The Senior International Fellowship Program, which awards fellowships to U.S. faculty members to study abroad, may have to be reduced substantially in 1981 and 1982 in order to free funds to maintain the other two fellowship programs.

- The FIC has discontinued the preparation of "scientific memoranda" and has phased out the support and management of extramural conferences except under those circumstances outlined in the new FIC referral guidelines. The funds from these activities will be applied to the two high-priority fellowship programs.

Program Directions

- The Scholars-in-Residence Program and the International Research Fellowship Program will remain prominent components of the FIC program. The Senior International Fellowship Program will be continued at a modest level.

- An International Issues Study Program will be initiated to conduct and support studies of the international aspects of biomedical research, research training, and the transfer of research results to health care systems. The planning phase will begin in 1981 and implementation will start in 1982.

- The FIC is seeking to establish an Advisory Council to provide advice on program development and to aid in the determination of priorities. In the meantime, the Center will rely on advice from the scientific community at large, augmented by guidance from the Institute Directors.

- Efforts to improve coordination and implementation of NIH's international programs will continue to be fostered through the newly established BID international representatives working group.

- Emphasis will continue on efforts to strengthen communications between the NIH and other agencies with direct responsibilities in the area of international health. Preliminary meetings have been held between the Director, FIC, and the Director, Office of International Health, to reaffirm the central coordinating role of the FIC.

- The FIC will strengthen its capability to collect, analyze, and distribute information on the biomedical research activities of other countries.

Action Items

The participation of the NIH in formal bilateral agreements has increased significantly in recent years. Clearly, an examination of the nature and extent of NIH involvement in such activities is warranted. As a preliminary step in anticipation of a full-scale study of this issue, the FIC will compile data on the total NIH funds devoted to activities conducted in support of bilateral agreements.

The FIC will examine the distribution of fellowship awards and plot the award history for the ten countries with the largest number of awards.

Fogarty International Center Fellowship Programs

Statement of Issue

The core program of the FIC traditionally has been its fellowship programs (Fogarty Scholars, International Research Fellowship Programs, and the Senior International Fellowship Program). The static budget of the FIC, plus the ever-increasing cost for each individual supported, has threatened to erode the very existence of the entire fellowship program. It is no longer possible to maintain a critical mass for the Fogarty Scholars Program, or to maintain the number of awards for the International Research Fellowship Program and the Senior Fellowship Program.

Discussion of Issue

The fellowship programs of the FIC constitute an important bridge between the U.S. scientific community and scientists in other countries. For the Fogarty Scholars Program to be successful, there should be a critical mass of at least ten scholars on the campus to permit fruitful interaction and cross-fertilization of their ideas.

For the International Research Fellowship Program to be balanced, it must provide opportunities for all the national nominating committees to have their best candidates accepted, and to be effective, it must also be possible to extend existing appointments without precluding new appointments. In addition, the FIC would like to be able to accommodate potential candidates from the increasing number of developing countries wanting to participate in this program.

For the Senior International Fellowship Program to remain viable, it is important to maintain a continuous flow of U.S. scientists to foreign countries. As science evolves and new research opportunities are created, especially in developing countries, the flow of U.S. scientists abroad should increase.

Alternatives and/or Suggested Position

In its fellowship programs, the FIC is faced with increased needs arising from both increased demands and new opportunities. Because of the unique value of each of these fellowship programs, FIC's first priority is to maintain the current number of awards. This will require additional resources, reflected in the FIC 1983 budget request, to cover the increased costs of stipends and other allowances due to inflation.

Without additional resources, the first priority of the FIC would be to maintain the Fogarty Scholars Program at the present level of ten. Since stipends must be increased to keep pace with inflation, it will be necessary to divert funds from the other two fellowship programs. The FIC is considering two strategies to deal with this problem. To avoid a drastic decrease in the very valuable International Research Fellowship Program, the FIC could redirect the necessary funds from the Senior International Fellowship Program. The second strategy is to reduce or eliminate International Research Fellowships available to industrialized nations with well-established and well-funded biomedical research communities.

International Issues Study Program

Statement of Issue

It has been determined that, to fully meet its mandate, the FIC should develop an International Issues Study Program addressed to the international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to health care systems.

Discussion of Issue

Up to the present, the FIC has supported very successful programs that facilitate worldwide exchange of ideas and information among members of the scientific community. The components of the FIC programs are designed to enable young, mid-career, and statesmen-scientists to participate in the bidirectional communication between the United States and other countries. There are, however, increasing demands on FIC programs as additional countries are broadening the spectrum of health-related questions of worldwide importance. In particular, the number of health issues is increasing considerably as developing nations are becoming more active members of the world community. It is not possible for the FIC or NIH to meet all these new challenges to the same extent as in the past. It appears unlikely that NIH resources will keep pace with the increase in needs and opportunities in biomedical research.

It is evident that, through the FIC, the NIH must delineate the extent and the direction of its involvement in world health problems. For this involvement to be successful, it must be within the realm of what the NIH does best, i.e., acquisition and dissemination of new knowledge from biomedical research. The FIC should determine how the existing NIH research capability can be used most effectively to identify the direction and provide the stimulus to find solutions to international health problems. This will be the goal of the International Issues Study Program. To accomplish this goal, the FIC must draw upon the best advice available. Establishment of an advisory mechanism and consultation with the Fogarty Scholars will make a major contribution to the planning and development of this program.

Alternatives and/or Suggested Position

The FIC is developing a plan to implement this Study Program, which is considered to be of the highest priority by both the Task Force that evaluated the FIC and, subsequently, by the Director, NIH, and the Director, FIC. In FY 1981, FIC is prepared to divert some of its resources to the planning phase of this activity. In FY 1982, additional resources will be necessary to begin implementing the Study Program. Staff will have to be increased initially by two individuals and subsequently by two more. Resources will be necessary to establish an advisory mechanism. It is expected that in FY 1983 the Study Program will reach full momentum.

NATIONAL LIBRARY OF MEDICINE

Director's Overview

Civilization advances through the communication of knowledge. The storage, retrieval, and processing of information is an essential resource for all social, cultural, and economic progress. Writing about the social framework of the present information society, Daniel Bell (a professor of sociology at Harvard University) describes four revolutions--speech, writing, printing, and telecommunications--that have changed the way people live:

> Speech was central to the hunting and gathering bands--the signals that allowed men to act together in common pursuits.
>
> Writing was the foundation of the first urban settlements in agricultural society--the basis of record keeping and the codified transmission of knowledge and skills.
>
> Printing was the thread of industrial society--the basis of widespread literacy and the foundation of mass education.
>
> Telecommunications--the ties of cable, radio, telegraph, telephone, television, and now, newer technologies--are the basis of an "information society."

Each of these revolutions was based on new ways of exchanging information--adapting new technologies for this purpose.

Knowledge is the source of progress and power. The library--from the earliest collection of stone tablets to the modern computerized information center--is the reservoir and repository of knowledge, and therefore, a critical resource for the functioning of society. The modern library also organizes and disseminates information in a socially acceptable way where rich and poor alike may share its benefits.

This has never been more true than in the late twentieth century, as we move into an era where information and knowledge, rather than agriculture or manufacturing, are becoming the strategic resources of our society. The information industry accounts for half of the U.S. labor force and 46 percent of the gross national product. Burgeoning high technology makes possible the transition to an information society. This is particularly important in the sciences.

The National Library of Medicine (NLM) is in the forefront in the transition from the printed word to computer-based communications technology which makes it easier to store, find, and retrieve medical information. The Library serves as the Nation's principal resource for information needed in biomedical research, health professional education, and the delivery of health care services. Users of the NLM include commercial and industrial organizations; hospitals, clinics and nursing homes; and academic institutions for medical, dental, and nursing education and research.

The results of research must be disseminated if they are to be of benefit to society. In fact, research is incomplete until it is documented and published. Research projects culminate in published results which are acquired, indexed, organized, and distributed by the NLM. The research scientist uses NLM resources to locate scientific and technical information. Access to the information is available either to a direct user of NLM or through its Regional Medical Library Network. Computerized data bases such as MEDLINE (MEDLARS Online) and TOXLINE (an online toxicology retrieval service--citations and abstracts) inform the scientist, educator, and practitioner where information exists.

The NLM saves health professionals from tedious thumbing of textbooks and journals by providing systematic, computer-assisted scans of the latest available information, no matter where it has been published. When a doctor, nurse, dentist, or veterinarian wants the latest information on a specific topic, the computerized bibliographic systems of the NLM stand ready to comb the current literature and extract a list of references and abstracts that guide the seeker swiftly to the most relevant articles for his purposes.

We are constantly improving these services. A new and improved information system called MEDLARS (Medical Literature Analysis and Retrieval System) III is currently being developed by NLM staff.

MEDLARS III will offer the biomedical community important new services such as a fully automated online interlibrary loan service which will ultimately allow the Nation's medical libraries to request journal articles online through our computer. Bibliographic searching will be simplified greatly; the user will be able to enter a single search to be run against multiple files using common English commands rather than artificial computer language.

NLM also provides specialized information services in toxicology and environmental health through online data bases such as TOXLINE and CHEMLINE (an online chemical dictionary), specialized search services at the Oak Ridge National Laboratory, and interagency projects such as the Chemical Substances Information Network. These services allow the producers of drugs and chemicals as well as health professionals to have rapid access to information about the effects on humans and the environment of drugs, chemicals, and other toxic substances.

In addition to its resources in Bethesda, NLM supports and coordinates a national network of 11 Regional Medical Libraries. They in turn are linked to 103 resource libraries and more than 3,000 local health sciences libraries. The network provides services such as lending materials between libraries, searching NLM's online bibliographic data bases, and providing acquisition and cataloging information to other libraries. In addition, it provides training and consultation to small institutions and encourages resource sharing among libraries. NLM shares the products of its labor-intensive cataloging efforts with libraries in the network, saving the Nation several million dollars per year. Each of the 11 Regional Medical Libraries coordinates information delivery services within its own region and cooperates with libraries throughout the network to provide nearly two million interlibrary loans annually.

NLM's grant programs under the Medical Library Assistance Act (MLAA) provide support for the establishment, development, and enhancement of health information services for health professionals. Grant assistance is used to maintain and improve the biomedical information network; to support research into new ways of representing, transmitting, and utilizing biomedical information; and to train information specialists and computer scientists. Computers in Medicine, a special initiative within this grant program, supports research and training in the computer sciences related to how biomedical knowledge can be organized so that clinicians faced with decisions about patient care can obtain information in an easy-to-use format.

The NLM dedicated the new Lister Hill Center Building in May 1980. It provides sophisticated resources for the Lister Hill National Center for Biomedical Communications and the National Medical Audiovisual Center (recently moved from Atlanta), as well as for several other NLM and NIH programs. The architectural and engineering plans for the renovation of the present library building have been completed and will improve the protection of the collection and safety of the readers.

The Lister Hill National Center for Biomedical Communications is the research and development arm of the National Library of Medicine. One major objective of the Center is to improve the manner in which books, journals, and audiovisual media are stored, retrieved, and used. Another principal effort of the Center is to develop "knowledge-based systems" which would provide specific, current information useful for patient care and health care delivery.

The National Medical Audiovisual Center's (NMAC) primary mission is to improve the transfer of health science information from research into practice through the use of audiovisuals. NMAC lends audiovisual materials to be used in health professional education and also supports an online data base of audiovisual materials known as AVLINE. The Center conducts workshops to train health science educators in the use of advanced educational technologies, assists in preparing educational materials, provides consultation on audiovisual facilities planning, and conducts research in how to improve the use of audiovisuals in health professional education.

The rapid growth of computer and communications technologies in our society presents challenges and opportunities for new ways of communicating knowledge. In addition to our present use of available technology, we are actively working with industry to investigate many newly emerging technologies, such as:

- Telefacsimile, which would allow copies of articles from journals or other documents to be sent across the country almost instantly;
- Electronic mail, enabling scientists to communicate with each other through computer terminals;
- Video disc technology for improved storage and retrieval of information;
- Computer-generated printing, to save money and increase timeliness of the scientific literature;
- Education through audiovisual devices, improving the training of health science students, scientists, and practitioners.

NLM's plans for FY 1981-83 are described below in priority order as follows:

- Improving library and information services.
- Developing MEDLARS III.
- Improving and expanding research and development.

Library and Information Services

FY 1981 Recent Accomplishments and Areas of Promise

In FY 1981, NLM's most important activity continues to be dedicated to the expansion and improvement of library and information services to the health science community. Examples of these accomplishments include:

- Building, maintaining, and providing access to an extensive collection of the world's biomedical literature.
- Acquiring, managing, and distributing audiovisuals and instructional media packages and training the health education community in their use.
- Expanding computer-based data banks and developing and operating information services in toxicology and environmental health.
- Improving the provision of health information to health professionals throughout the Nation through the grant mechanism.
- Coordinating the Regional Medical Library (RML) Network. Continuation of the RML Network is assured through FY 1982 by renewal of the Medical Library Assistance Act.
- Replacing the manual card catalog with a computer-output microfilm catalog as a step toward the ultimate online catalog.

- Converting NLM's computer system from one of limited capacity to a new system which increases NLM's computer capacity nearly threefold. Acquisition of this sytem resulted in actual cost savings to the Government of approximately $9 million while greatly enhancing NLM's ability to provide service to its users.

FY 1982 Priorities

In FY 1982, NLM will emphasize:

- Providing reference and bibliographic services through NLM and the Regional Medical Library (RML) Network to meet growing demands.

- Improving information services in toxicology and environmental health.

- Improving cooperation with the Library of Congress and the National Agricultural Library.

- Lending audiovisual materials for health professional education, supporting the AVLINE data base, training health science educators in the use of advanced educational technologies, producing educational materials, and providing consultation on audiovisual facilities planning through the NMAC.

FY 1983 Plans

At the FY 1983 request level, NLM will be able to maintain basic services at the same level as FY 1982.

- Despite the demand for increased services such as computer searches and document delivery to readers and the constantly increasing cost of books and journals, NLM will maintain its acquisitions and library services. The scope and coverage of its collection will be broadened to include such areas as the behavioral sciences and public health policy.

- The services of the RML program will be sustained.

- Audiovisual services will be maintained. The use of instructional technologies in the health professions will be enhanced.

- Information services in toxicology and environmental health will be maintained; however, an important new initiative to provide information to industry and government agencies regarding chemical hazards, although desirable, will not be undertaken.

MEDLARS III

FY 1981 Recent Accomplishments and Areas of Promise

MEDLARS (Medical Literature·Analysis and Retrieval System) III is directed toward improving and enhancing NLM's services to the biomedical community.

Major activities in FY 1981 include:

- Assembly of an in-house program management and system development team.
- Completion of a system development plan which will address MEDLARS III capabilities, technology considerations, alternative approaches, transition to the new system, testing, documentation, resources, and time tables.
- Providing new technical processing capabilities such as further automation of indexing and cataloging.

FY 1982 Priorities

The major efforts in FY 1982 will be to:

- Develop by December 1981 an RFP (request for proposal) for the design of MEDLARS III.
- Incorporate into MEDLARS III recent library automation systems developed through research at NLM.

FY 1983 Plans

The FY 1983 request will allow NLM to complete the MEDLARS III development on schedule in FY 1983.

Research and Development

FY 1981 Recent Accomplishments and Areas of Promise

The third priority of the NLM is to improve and expand R&D in the Lister Hill Center, the National Medical Audiovisual Center, and extramural programs. The fundamental research and development problem of the Library is the same as it was more than a century ago: to deliver appropriate information, in a readily understood format, when it is needed, to a health professional capable of effectively using it for the benefit of the patient. From Billings' monumental development of Index Medicus to current efforts to develop MEDLARS III, all of the Library's research has been and is now directed at some aspect of this problem:

- The Lister Hill Center (LHC) knowledge base program is designed to create through analysis and synthesis appropriate information, while much of the research of the National Medical Audiovisual Center is directed toward creating readily understood formats.

- The LHC is also actively engaged in both the problems of information retrieval and information delivery while much of the Computers in Medicine grant program is supporting investigators in universities who are pursuing automated means of facilitating the health professionals' appropriate use of information for the benefit of the patient.

These research objectives can only be achieved through the continued support of basic inquiries into the structure of knowledge and its representation.

FY 1982 Priorities

A major priority for FY 1982 is to continue support for the Computers in Medicine Program. Computers in Medicine researchers are:

- Developing automated files of information about topics such as acute poisoning and coronary artery disease that will help health professionals by extending memory.

- Developing automated interactive systems to help health professionals focus on the information available in general internal medicine and general clinical decision-making.

- Conducting basic investigations in knowledge representation.

The FY 1982 budget does not allow any new awards to be made in this program.

The Lister Hill Center will continue its major research in:

- Knowledge base building.

- Knowledge representation.

- Information retrieval.

- Information storage and dissemination.

The NMAC will continue its efforts to develop:

- More effective and readily understood formats for presentation of information to health professionals under various circumstances.

- Applications of electronic and communications technology to create a presentation of information which is free of the restrictions of any particular medium.

- Applications of technologies to create more effective representation and to educate health professional educators in more effective use of educational technology.

FY 1983 Plans

At the FY 1983 request level, NLM will be able to enhance its intramural research programs in new methods for the delivery of relevant information to the biomedical community, but will not be able to develop new research efforts or fund new Computers in Medicine awards.

Potential Impact of Program Changes on Three-Year Period, FY 1983-85

Rapid change is a major theme of our times. To assess the implications of changes in the biomedical and information sciences on the continuing vitality and growth of our institutions is a critical and urgent matter today. We are all increasingly familiar with the technological aspects of this change. The press is full of the information age technology, the hardware associated with the new order: word processors, home microcomputers, videodisc libraries, electronic mail, etc. But the new order brings more than new gadgetry and new communications formats. Industrial production is shifting away from the developed countries. Developed countries are shifting to an information-based society, where the strategic resource is knowledge and data. More decentralization and less centralization of institutions is occurring. For example, big associations are breaking up into smaller special interest groups. More and more, local initiatives inform and shape national programs. Burgeoning high technology is accompanied by growth in personalized services; for example, high technology in medicine and the family practitioner and neighborhood clinic movements. This calls for a reconceptualization of information: how it is used, managed, and valued. The need for increasing quantities of timely and understandable information is intensifying.

The impact of these forces on libraries, society's traditional information storage and retrieval centers, is apt to be profound. The changes within the NLM described in this document attempt to be responsive to these societal changes. NLM has a critical role as a resource for health education, research, and practice in the 1980s. Given the necessary resources, the National Library of Medicine can become a center of research and development to facilitate information transfer, so that the discoveries in the biomedical research laboratories may more rapidly and effectively impact on the direct and immediate care of the patient. Innovations such as MEDLARS III and the results of research in biomedical information transfer will enhance this role.

NLM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director
National Library of Medicine

DATE: February 12, 1981

FROM : Director
National Institutes of Health

SUBJECT: Planning/Appropriation Briefing Session

I appreciated the opportunity to discuss with you and your staff the Bureau's plans for the next several years, as well as some of the issues you will have to deal with during that time. Attached are the summary notes, in the new format, of the briefing session. I have asked that copies of the issue papers which you prepared for the session be circulated with these notes to the other Institutes for their information.

The Library is the reservoir and repository of knowledge and serves as the nation's principal resource for information needed in biomedical research, health professional education and the delivery of health care services. The NLM continues to be in the forefront in the transition from the printed word to computer-based technology which makes it easier to store, find, retrieve and disseminate medical information. Once the briefing sessions are complete and tentative budget ceilings for 1983 are established, Kurt Habel will be in touch with you concerning fuller development of your research plan.

Donald S. Fredrickson, M.D.

Attachments

cc:
Review Participants
BID Directors
BID Planning and Evaluation Officers
BID Budget Officers
OD Staff
PPE Directors
Mr. Mansfield
Mr. Miller

HIGHLIGHTS AND ACTION ITEMS OF THE PLANNING/APPROPRIATION BRIEFING SESSION WITH THE DIRECTOR, NIH

Highlights

Introduction

Although the NLM appropriation has doubled in the last 14 years, it remains at about the 1968 level when measured in terms of constant dollars.

Information and computer-based bibliographic services have increased substantially in the past ten years; yet current on-board staff remains at about 1970 levels.

Impact of Stabilization

No NLM activities are included under the stabilization initiative.

The stabilization of NIH research project grants can adversely impact upon the NLM's service and research programs during periods of economic restraint, to the extent that funds must be diverted from other sources to meet the NIH stabilization commitment.

Medical Library Assistance Act

The MLAA, NLM's only source of grant authority, was initiated in 1965. The current extension terminates at the end of FY 1981, and a three year extension has been proposed. The present economic and political atmosphere suggests that a strong defense of the MLAA may be necessary.

Six programs are covered by the Act:

- Regional Medical Libraries. This is NLM's highest priority program authorized by the MLAA; it consists of a national network of 11 Regional Libraries which provide access to information in support of health services delivery, education, and research by cooperative sharing of resources.

- Training. This high priority program has shifted its focus over the years from training health science librarians to training health science professionals in the use of computers in medicine.

- Research. This is another high-priority program and provides support for investigations of new ways of organizing, representing, transmitting, and utilizing information, including Research Career Development Awards, New Investigator Awards, and program projects under the Computers in Medicine Program. This is a relatively new and modest effort, of major importance to helping the health professional gain more efficient and effective access to health-related information.

- Resource. This program, also of high priority, provides support to academic institutions and hospitals in the form of both small improvement grants, with a matching requirement, to strengthen existing libraries, and larger project grants to develop library resources and support resource sharing and outreach activities.

- The Special Scientific Projects and Publication Programs provide grant support for the development of scholarly treatises and the publication of monographs that would not be published by the private sector because of their limited audience and lack of commercial viability.

Office of Technology Assessment (OTA) Study

The House Subcommittee on Health and the Environment requested the OTA to undertake a study of the methods of medical technology assessment, the dissemination of information developed by technology assessment, and the uses of the results of technology assessment by Federal programs. This study will take 15 months to complete and will include an evaluation of MEDLINE. A close examination of the indexing process and the validity and relevance of retrieved articles will be made. The NLM is not aware of any serious problems with or complaints about the quality of its services. However, NLM is concerned that the OTA study is based on some misleading premises and that no experts in the field of library and information science are serving on the staff of the study.

Proposed OSHA Regulations

NLM expressed concern about being included in proposed Occupational Safety and Health Administration (OSHA) regulations requiring manufacturers and importers of potentially toxic materials to obtain computer searches and literature from the NLM. The Library suggests that the use of its services be optional rather than mandatory.

Priorities

NLM has established priorities in three general areas, as follows:

- Improving Library and Information Services. In 1982, emphasis will be placed upon providing reference and bibliographic services to meet growing demands, replacing the manual card catalog with a computer-output microfilm catalog as an interim measure in the development of a fully automated online catalog, improving toxicology information services, and providing audiovisual services. With additional funding in 1983, the scope of the TOXLINE and Toxicology Data Bank would be broadened to include information on hazardous waste management and chemical hazards in the laboratory, online retrieval programs used to access NLM toxicology information services would be revised and improved, and the Regional Medical Library Program would receive additional support. The Laboratory Animal Data Base will be eliminated or transferred to another Federal or private agency when current funds are expended.

- MEDLARS III. In 1982, a RFP will be developed for the design of the system, and recent library automation systems developed through research at NLM will be incorporated into the system. In 1983, an additional $1.5 million will be required to proceed on schedule and to implement the basic system by September 1983. Once fully implemented, the improved capabilities of this system should result in about $5 million in savings nationwide each year by replacing current manual card cataloging as well as improving document processing and distribution through an automated system.

- Research and Development. In 1982, current activities under way at both LHC and NMAC will continue at the present level, and no new awards can be made in the Computers in Medicine Program. With additional funds in 1983, LHC R&D efforts will be expanded and new awards will be made in the Computers in Medicine Program.

Action Item

As we continue to face stringent resource constraints, it becomes increasingly important to examine requirements for positions. This is particularly true for an organization such as the NLM, where demands for service continue to increase and technological innovation can alter staffing requirements. Please examine carefully your position requirements in this context and be prepared to discuss this in depth at your spring/fall program review.

MLAA

Statement of Issue

The MLAA (currently authorized by Biomedical Research and Research Training Amendments of 1978--P.L. 95-622), first established in 1965, terminated with FY 1981. [Ed. note: The Act has been extended through FY 1982, and a proposal for reauthorization has been submitted for FY 1983 and beyond.]

Discussion of Issue

There have been five previous extensions of the MLAA. Both the Legislative and the Executive branches have supported the continuation of the legislation, agreeing that the NLM's extramural grant activities are effective.

The present economic and political atmosphere suggests that a strong defense of the MLAA may be necessary in order to sustain our current program. For the first time we will be appearing before two new committee chairmen who need to be informed about the benefits of the MLAA and its role in improving biomedical information services in the country. They must be convinced that improved biomedical communication is essential to advancing medical research, education, and practice.

Recent budgetary actions which reduce the MLAA programs by 14 percent in 1982 may indicate a lack of understanding of the program's impact on improving library and information services, particularly at the hospital library level of the network.

Alternatives and/or Suggested Position

The six programs authorized by the MLAA are not general support mechanisms for unrelated library activities but are part of a coordinated program related to the goals and objectives of the National Library of Medicine and, ultimately, to the accomplishment of the NIH and Department mission. The dissemination of biomedical information in many formats to all health professionals and paraprofessionals throughout the United States is an important part of the effort to help make all types of health education programs more effective. This information dissemination is also critical to other areas of health concerns such as research, technology transfer, and clinical decision-making.

All of the MLAA programs provide extramural support to activities that directly or indirectly improve the communication of health information. They provide direct assistance toward the maintenance and continued development of a decentralized and fiscally cooperative biomedical information network, and they strengthen the network indirectly by supplementing its health knowledge base. They support investigations of new ways of organizing, representing, transmitting, and utilizing information; and they foster an expansion of human resources with competencies in information science research and in the effective combining of medicine and the computer sciences.

NLM, through the MLAA, has done much to address the wide imbalance that previously existed between the needs of the health professional and the medical library resources available to satisfy those needs. The task continues, for the medical information explosion calls for new networks, methodologies, technologies, and trained manpower to meet the information service needs of medical science.

Office of Technology Assessment Study

Statement of Issue

Is the NLM MEDLINE system adequately responsive to the need to disseminate technology assessment information to practitioners and public officials?

Discussion of Issue

As part of the House consideration of the reauthorization of the National Center for Health Care Technology and related authorities, such as those of the National Library of Medicine, Congressman Waxman requested that the Office of Technology Assessment (OTA) undertake a study of the methods of medical technology assessment, the dissemination of information developed by technology assessment, and the uses of the results of technology assessment by Federal programs. He has requested OTA to include an evaluation of MEDLINE in this study.

Mr. Waxman's Committee appears to be interested in the means by which technology assessment information is disseminated to practitioners and public officials who make decisions on the basis of such information. The contention is that there are some serious problems with the MEDLINE system. A close examination will be made of the indexing process and the validity and relevance of retrieved articles.

Alternatives and/or Suggested Position

NLM recognizes there can always be improvements in any system and welcomes constructive suggestions to improving MEDLINE. It should be recognized that NLM currently has over 1,500 institutions that have generated over three million searches in the past two years. Despite this large volume of use, we do not have any serious complaints about the quality of the service. The contention, therefore, that there are serious problems with MEDLARS is not borne out with any clear evidence.

It would appear that the OTA review was prompted by the "Medical Practice and Information Demonstration Project," which claimed that much of the information being published is not valid and has little relevance to medical practice, and that much that is relevant is not readily accessible. A PHS panel reviewing the study, however, questioned the methodological approach used, particularly as it related to the MEDLARS system.

Status of Issue on May 4, 1981

NLM has received two draft reports from OTA: a staff paper on NLM, dated March 16, 1981, and a separate chapter entitled "Biomedical and Health Services Research Literature and Bibliographic Information Storage and Retrieval Systems in the Private Sector," dated February 22, 1981. The OTA staff paper presents a reasonable general description of NLM activities. However, it is flawed by a number of statements which appear to be unsupported by facts or based on an incomplete understanding of NLM's programs. Instead of providing background information to the Congress for the reauthorization of the MLAA, the study concentrates on trying to demonstrate inadequacies in MEDLARS and other NLM programs. The chapter on the private sector is superficial, consisting of simple, unanalyzed descriptions of interviews with marketing agents of data base proprietors. NLM is compiling a detailed response to be transmitted to OTA.

NLM Involvement in HHS Health Research Planning Initiatives

The National Library of Medicine does not have lead agency responsibility for any of the HHS Health Research Planning Initiatives. However, NLM does provide information support for the National Toxicology Program. NLM's Lister Hill Center has been suggested as a participating organization for the proposed initiative on the prevention of birth defects, because of its work on a human genetics knowledge base.

In a broader sense, NLM supports all of the initiatives by serving as the Nation's principal resource for information in support of biomedical research, health professional education, and the delivery of health care services in both the private and the public sectors. Users include commercial and industrial organizations; hospitals and other health care institutions; academic institutions such as medical, dental, and nursing schools; and research organizations.

The research scientist uses NLM resources to locate scientific and technical information (either as a direct user of NLM or through the Regional Medical Library Network) through data bases such as MEDLINE and TOXLINE. The results of research must be disseminated to the scientific community if they are to be effectively utilized. Research projects culminate in published results, which are acquired, organized, and distributed by the NLM. The Library provides bibliographic references to the literature through printed indexes and special bibliographies and the actual article can be secured through a national document delivery network. As an example of these services, NLM provides 1.4 million computer searches of its data bases, such as MEDLINE, to over 1,500 user institutions each year. NLM online bibliographic search services account for roughly half of all of the computer-based searching in the United States. Its library network provides nearly two million loans annually.

PROGRAM PERFORMANCE SUMMARY

MEDICAL LIBRARY ASSISTANT ACT PROGRAM

Program Description

The Problem Being Addressed

The national investment in medical research and development is realized only to the extent that the results--information and new knowledge--are known and utilized. "Transfer of information is an inseparable part of research and development (and all those involved) must accept responsibility for the transfer . . . in the same degree and spirit that they accept responsibility for research and development itself."(1) The fundamental purpose of the National Library of Medicine (NLM) is to improve the health of the American people by providing access to health knowledge. The information needs of the total health community--scientists, educators, health professionals, students, and administrators--can be effectively and efficiently satisfied by a coordinated network of health information and library systems. The Medical Library Assistance Act (MLAA) enables NLM to fulfill its purpose nationally by authorizing grants to develop information access mechanisms linking individuals and institutions at local, regional, and national levels.

The NLM Extramural Programs Division has exclusive responsibility for administration of the MLAA grants programs.* The overall goals of the Division's MLAA activities are (1) to improve and expand established and proven mechanisms of information transfer--specifically, health science libraries--and to develop a national library network; (2) to support the analysis and synthesis of health events and information; and (3) to create new, nontraditional methods of information access and utilization based on a comprehensive understanding of the dynamics of health information. The various grant and contract programs authorized by the NLAA are all utilized to achieve these goals.

Legislative History

The programs authorized by the MLAA in 1965 reflected the strengths and weaknesses of the biomedical information environment. On the strength side, there existed a health science library community with a strong spirit of cooperation, and the NLM to provide a leadership focal point. On the other side, the weak status of health science libraries was well documented, and it was common knowledge that increasing demands for information services, responding to the large growth in health research and education, could not be met by librarians.(2) A critical imbalance existed. The MLAA provided the means to unite librarians and libraries, health professionals and institutions, and the NLM in achieving the common goal of improving health information access.

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*NLM supports other non-MLAA extramural activities by contracts from other Divisions of the Library.

The MLAA was enacted for five years and, by extensions, is presently authorized through FY 1982. The legislative history is summarized in Table 1 below. The Act has been modified only slightly during the past 15 years, except for the repeal of construction authority in 1974. The remaining programs originally authorized continue to prove valuable in achieving program objectives.

In the 15 completed years of the MLAA (FY 1966-80), $118.5 million has been awarded in almost 3,000 grants and contracts (an average of $8 million each year for 200 awards). Actual appropriations represented 40 percent of funds authorized. Nearly 70 percent of funds available in an average year are typically committed to project continuations.

Program Funding and Staffing FY 1978-82

MLAA program activity for FY 1978-81 and estimated for FY 1982 are shown in Table 2. NLM staff involved in MLAA programs includes 26 professional and clerical persons, or about 5 percent of the total NLM staff. The MLAA budget is about 20 percent of the total NLM budget.

Program Objectives and Activities

In addition to the overall extramural program objectives described earlier, the objectives and current activities for each program individually are as follows:

Library Resource Grants

Resource Project Grants assist the established health science library to develop new services or to improve and expand existing ones. Projects that have impact beyond the grantee institution, such as consortia or Statewide networks, are emphasized.

Two examples provide ample evidence of the types and importance of resources developed. The Consortium for Health Information, in Pennsylvania, was previously supported by a resource project grant and is now supported locally. A three-year project grant had made it possible to recruit a full-time coordinator, who successfully implemented a variety of activities for coordinated information services. Union lists facilitated sharing; new MEDLINE terminals were installed for the consortium; and efficient loan and delivery arrangements expedited access to print and nonprint materials.

A project grant also supports a highly significant national resource in the field of bioethics developed by Georgetown University, including the "Bibliography of Bioethics" and an extensive thesaurus covering this field. Previously, the data gathered by the grant-developed bioethics information retrieval system had been made available online, through BIOETHICSLINE, to all

NLM

Table 1

Medical Library Assistance Act

Legislative History
(Dollars in Thousands)

Act	Appropriation
PL 89-291 Medical Library Assistance Act FY 1966-70	$40,800
PL 91-212 Extension FY 1971-73	21,376
PL 93-45 Extension FY 1974	7,029
PL 93-353 Extension FY 1975-77	22,694
PL 95-83 Extension FY 1978	8,983
PL 95-622 Extension FY 1979-81	28,741
PL 97-35 Extension FY 1982	7,500

Table 2

Medical Library Assistance Act Program Funding
(Dollars in Thousands)

	FY 1978		FY 1979		FY 1980		FY 1981 est.		FY 1982 est.	
	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.
Programs										
Grants										
Resource	52	$2,013	79	$2,008	73	$1,596	6	$1,641	41	$1,203
Research	14	1,176	22	1,648	32	2,794	31	2,774	26	2,353
Training	11	1,459	10	1,472	10	1,638	10	1,308	8	900
Publication	47	1,069	36	795	35	787	34	818	18	521
Special scientific projects	7	248	7	215	6	142	7	290	2	23
Contracts										
Regional medical libraries	9	3,018	9	2,848	8	2,967	9	2,999	10	2,500
TOTAL	140	$8,983	163	$8,986	164	$9,924	147	$9,830	105	$7,500

MEDLINE users. Current grant support also enhances the probability of fiscal self-sufficiency for continued production of this vital bibliography.

Resource Improvement Grants assist in the establishment of basic library services in health institutions, or in a consortium of health institutions. Support for library consortia encourages resource sharing and other cooperative activities.

As an example, the Central Coast Health Sciences Library Consortium, in a four-county area along the California coast, has a membership that includes hospitals, colleges and universities, and a public library system. Support from the MLAA is being used to build up library resources at the community level to meet the day-to-day information needs of physicians and other medical personnel. In addition, health science libraries are being encouraged by means of the consortium award to share their resources and services in an effective manner.

Research Grants

Research audits support investigations leading to new knowledge about health information access, retrieval, and use. They also support the development of practical applications from theoretical insights and the demonstration of new technologies under operating conditions.

A subset of the Research program is the Computers-in-Medicine program, which supports studies of new applications of computer technology in health care settings, of decision-making processes in health practice, and of new ways to assist health professionals to draw upon health knowledge and research results in the evaluation and management of disease. Studies include basic research into fundamental issues of health information, as well as the application of research findings.

Many NLM principal investigators and project team members are gaining recognition for their work and are assuming positions of professional leadership. The following illustrate research activities.

Dr. Donald Walker, SRI International, has just published a comprehensive article on new developments in computer-based procedures for understanding information use in the September issue of the *Journal of the American Society for Information Science*. Dr. Walker's NLM-sponsored research in natural language access to medical text is included in the article, entitled, "The Organization and Use of Information: Contributions of Information Science, Computational Linguistics and Artifical Intelligence."

A program project at the Massachusetts Institute of Technology, dire ted by Prof. Peter Szolovits, addresses several fundamental issues in clinical decision-making from the perspective of artificial intelligence.

The work of Prof. Belver Griffith of Drexel University and his colleagues shows that analysis of scientific paper citations, as revealed in a bibliographic data base, can provide insights about science as a social undertaking. His results are useful to information managers as well as to students of scientific communication.

Dr. Howard Beich, Beth Israel Hospital, Boston, is successfully developing a most effective supplementation of MEDLINE. The net contribution of Bleich's system "Paper Chase" is to provide a means of searching for citations known to be held locally, particularly where more exhaustive searches of MEDLINE are not required.

Training Grants

Grants assist in the training of health communications specialists required for the efficient and effective organization and dissemination of health science information. The Training Grants Program currently emphasizes training for the better integration of computer technology into all phases of medicine.

Sites for the training are the University of California at San Francisco; Duke University (Durham, N.C.); the University of Alabama (Birmingham); Ohio State University (Columbus); the University of Minnesota (Minneapolis); Case Western Reserve University (Cleveland, Ohio); the University of Missouri at Columbia; the University of Illinois (Urbana); the University of Virginia (Charlottesville); and the New England Medical Center Hospital (Boston, Mass.).

Publication Grants

These grants assist in the preparation, production, and dissemination of biomedical scientific publications of a nonprofit nature. Selective, short-term support is provided for critical reviews and monographs on special areas of medical research and practice; publications on biomedical communications and in library and information science; secondary literature tools in the health sciences (biomedical handbooks, guides, abstracts, bibliographies, etc.); proceedings of scientifically significant symposia; periodical publications; translations of current foreign biomedical monographs; and scholarly research monographs in the history of medicine.

Among the studies published recently that had received earlier support in the Publication Grant Program was L. Grinspoon and J.B. Bakalar's "Psychedelic Drugs Reconsidered" (New York, Basic Books, 1980). Another monograph published with NLM support for manuscript preparation was L.S. Taylor's "Organization for Radiation Protection" (Washington, D.C., U.S. Department of Energy, 1979), a mammoth historical report of the organized development of radiation protection standards nationally and internationally.

The Library's continuing interest in the ethics of biomedical research and medical practice is also evidenced in a three-year pilot grant to assist a new periodical, "IRB, A Review of Human Subjects Research." It is the only periodical exclusively devoted to this increasingly important subject. The Library's support for medical librarianship was reflected in the publication of Prof. Alan M. Rees and Dr. Susan Y. Crawford's "Directory of Health

Sciences Libraries in the United States, 1979" (Cleveland, Case Western Reserve University, 1980).

Special Scientific Project Grants

These grants support the preparation of scholarly, booklength interpretive analyses by highly qualified investigators to identify, analyze, and document the existing literature on major areas of biomedical concern. In addition, the grants support treatises in problem areas where health affairs intersect with other social domains, such as public policy, law, bioethics, and computer science. One of the projects was published recently: Robert F. Rushmer, M.D., "National Priorities for Health: Past, Present and Projected" (New York, John Wiley & Sons, 1980). Another awardee, William C. Stratmann, Ph.D., of the University of Rochester, has completed a manuscript on evaluating hospital-based ambulatory care.

Regional Medical Library Contracts

These contracts support the development and maintenance of a national system of health science libraries--the Regional Medical Library Network--to improve and expand health information access for all health personnel through programs of cooperation and sharing. The Network currently comprises 11 Regional Medical Libraries, more than 100 resource libraries (at medical schools), and some 3,000 hospital and other community health institution libraries, coordinated by the NLM. Each of the 11 RML's coordinates information delivery services within its own region and cooperates with libraries throughout the network to provide nearly 2 million interlibrary loans annually. These loans facilitate and expedite the provision of critically needed information to the many health professionals who request the service. Other services include bibliographic access to journal and monograph information, cooperative acquisitions, cataloging, consultation, training, workshops, and continuing education programs.

Evidence of Program Performance

Over the 15-year period of the MLAA, patterns of program growth and change are seen in the kinds of projects undertaken, in the individual grant program expenditures, and in program direction. Although there has not been an explicit, lock-step plan of development (the diversity of the population and the magnitude of the tasks preclude it), an implicit order of evolution is found in various writings of the early 1960s, in language contained in the legislation, and in the sequence of necessary stages of program development. Some developmental order is necessary, for the limited program funds in consideration of the needs have required a careful distribution of MLAA funds to assure the highest possible success.

Program staff need information on progress, and there is a continuous record of Extramural Programs assessment and evaluation studies, as well as an established staff operation to support the studies. NLM's Extramural Programs maintain a management information system that contains program data for effective administration, but which is also regularly exploited for evaluation and planning. Eleven separate studies have been completed over the year, three are currently active, and two are planned to begin in the near future. These studies are summarized in Attachment A. All have provided information utilized for evaluation and program change.

Evaluations of individual program or separate activities within programs have documented achievements, but programmatic successes are not necessarily ends in themselves. The degree of accomplishing overall MLAA goals may not be readily observable in program data presentations. It is now apparent that the results of the two assessments of the full MLAA, one for the first 5 years and one for the next 10 years resulting in a 15-year record, combined with the results from individual program evaluations and evaluative studies from other sources will provide the opportunity to measure success in achieving overall goals.(3,4) For example, the following paragraphs summarize evaluation results that will contribute to the assessment of achieving the goal "to improve and expand established and proven mechanisms of information transfer"--specifically, health science libraries.

Support of Library Resources and Services

The weak status of health science libraries prior to 1965 required that initial program emphasis be placed on the improvement of library resources, the necessary prerequisite to services. The assessment of MLAA activity for the first five years showed that Library Resource Grant funds had been used effectively for resources development. Over 50 percent of the funds were used to acquire journals, books, and other information materials; 24 percent supported increases in staff; and 16 percent were used to purchase equipment. An estimate was made of the distribution of all MLAA program funds. Fifty-five percent were utilized for materials and 8 percent for services.

The Act was modified with a change in Resource Grant mechanisms. The result has been a measurable decrease in Project Grant support for collection development and a significant increase in service activities. The assessment of the next 10 years of the Act shows that overall MLAA support for materials had decreased to 19 percent, while support for services increased to 38 percent. The specific objective to emphasize services by exploiting the investment in library resources made in the first five years was achieved during the extension of the Act.

Support of Local Health Science Libraries

The analysis of FY 1966-70 expenditures showed that few awards were received by the smaller community health institutions, and that this part of the library community was insufficiently developed. One estimate indicated as few as 500-600 adequate libraries existed, about 7 percent of the potential community-level population. It was important to develop this level: the libraries would serve a large health professional population, and would provide the foundation to extend the Regional Medical Library Network. The first extension of the Act modified the Library Resource Grant program to allow for needed support mechanisms. The Resource Improvement Grant Program was created(5) and, as a result of a 1976 evaluation, was modified to promote Consortium Grants.(6)

As a result, a larger proportion of Resource Grant awards (15 percent increase) went to hospitals of all sizes in the next 10 years. An analysis of award data to hospitals by bed size shows a 211 percent increase in the average annual award to hospitals of fewer than 300 beds, for an overall 703 percent increase in funds from FY 1966-70 to FY 1971-80. In addition, an analysis of the members of consortium grants shows they are predominantly smaller institutions.

Sustaining Library Improvements

The permanence of improvements must be assured if the goal of a national biomedical library network is to be achieved: network stability depends upon well-established libraries. Consequently, institutional maintenance of grant-supported improvements is a crucial indicator not only of individual project success and grant program impact, but also of the attainment of prerequisite stages of library development necessary for network evolution.

Maintenance of grant-supported improvement was specifically measured as a part of the Improvement Grant program evaluation by comparing awardees with unsuccessful applicants and a control group of nonapplicants on key variables such as budget, personnel, and collection. It was found that awardees outperformed both other groups, and continued growth was stimulated in institutions regardless of location or size. It was found that the dividend from the $3,000 grant investment was an average library operational budget of better than $12,000.

A study by a non-Federal investigator documented improvements in medical school libraries(7). Integrating data from many sources showed significant growth over a 15-year period through 1975, the medical school library emerging as the leading center of growth by all variables measured. The MLAA was credited with providing the greatest impetus for change in the history of health sciences librarianship.

The investment of MLAA funds in the development of library resources has established a firm base on which other improvements and elaborations can be advanced.

Regional Medical Library (RML) Evaluation

NLM is currently involved in a major effort to evaluate the RML network. The purpose of this study is to supply the Library with data regarding the success of network libraries in providing services, in attaining optimal levels of performance, and in carrying out NLM policies. The study will also produce information to aid in determining whether regional boundaries should be changed and will examine new concepts and programs that should be considered or tested to meet RML objectives. As a result of the study, a management decision will be made on how to improve the effectiveness of the network.

Additional Information and Data

Relevant data other than the examples described are available from other MLAA programs and will be used in a subsequent comprehensive assessment of MLAA goals.

Major Issues and Problems

Organizations within the Administration have not identified major problems regarding the MLAA grant programs. As a unique service to the total health community, the program need is universally recognized and continues to enjoy endorsement by the Administration.

No single consentaneous issue of interest groups or the programs' constituency can be identified as a current problem. In previous years one major issue of interest to a numerically large part of the Resource Grant program constituency--hospital libraries--related to their perception that their needs were not being met nor their concerns heard. As a consequence an NLM conference was arranged. Eleven representative librarians met in Bethesda to air issues and make recommendations. The conference not only ameliorated concerns of hospital librarians, but also resulted in a number of programmatic changes in the NLM functions.

Critical Issues Relating to Program Performance

MLAA Legislation

The most immediate, critical issues before NLM is the renewal of authority for the MLAA, and the appropriation of adequate funds. P.L. 97-35 has extended the Act for one year through FY 1982, but for a $7.5 million dollar appropriation level, approximately a 24 percent reduction from FY 1981. It is vitally important to protect the investment made in improving libraries and health information access, and to continue the process of training personnel for an effective national mechanism of health information transfer. Stability of the MLAA program will hopefully be assured through a multiple-year authority and a reasonable, responsive level of appropriation.

Documentation

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Medical Library Assistance Act

Past Evaluation Studies
(From 1970)

Program	Date & investigator*	Objective	Results
MLAA	1970 NLM staff (Ref. 3)	Analysis and assessment of the MLAA programs.	MLAA emphasis changed to services from resource development; RML funding changed to contracts; numerous administrative changes.
Training (librarian)	1971 NLM staff, contract (Ref. 8)	(1) Evaluate training programs for librarians; (2) Forecast (Delphi) future to assist in modifying programs.	MLS training judged to have satisfied original manpower needs. Librarian training phased out; training redirected to computer technology.
SSP	1975-76 NLM staff and consultants	Evaluate program needs: identify ways to improve.	New guidelines and a screening-out procedure. Resulting increase in number and quality of applications.
Research	1977 Sherman Committee (Ref. 9)	Evaluate programs; recommend improvements.	New programs; research career development awards, new investigator awards, research program projects in computer medicine.

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*Reference numbers refer to Documentation section.

Medical Library Assistance Act

Past Evaluation Studies
(From 1970)

Program	Date & investigator*	Objective	Results
Resource project	1974-75 NLM staff and consultants	Develop guidelines for audio-visual and learning resource center projects.	Guidelines adopted 1974; improved applications.
Resource improvement	1974-75 NLM staff (Ref. 6)	Evaluate program and need; recommend changes.	Program was changed to emphasize consortia and sharing; support level increased. Program judged successful and needed. (Modified following hospital librarians conf., 1978.)
RML	1972 NLM staff, board of regents, consultants	Evaluate RML program status and recommend changes.	Site visits to each RML during 1972-74. Reports made available after each visit; final report in 1974. Recommendations for RML planning, advisory bodies, inter-RML communication, and interaction of RML and NLM.
PHS support of biomedical communication activities	1978 consultants	Administrative study to aid EP staff. Identify PHS components and levels of support in biomedical communications categories. Identify areas of interagency cooperation.	Finding that NLM is virtually alone in PHS in sponsoring biomedical communications R&D based on PHS data. Extensive PHS support for clearinghouses, publications, bibliographies, etc.

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*Reference number refers to Documentation section.

Medical Library Assistance Act

Past Evaluation Studies
(From 1970)

Program	Date & investigator*	Objective	Results
Publications	1974 NLM staff and consultants	Evaluate program; recommend improvement.	Program emphasis changed to lower cost, shorter term projects. Emphasis on critical reviews; early publication date; projects that explore improvement in health care delivery and critically examine health profession trends.
Resource project	1971 NLM staff and consultants (Ref. 5)	Automation project criteria and guidelines development based on review of projects and status of field.	Automation supportable, guidelines implemented as policy.
Research and resource	1980 NLM staff (Ref. 10)	Measuring the communication of results from NLM grant-supported library projects.	Found grantees were reporting results extensively in a variety of written formats and oral presentations.

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*Reference numbers refer to Documentation section.

Medical Library Assistance Act

Active Evaluation Studies

Program	Investigator*	Objective
MLAA	NLM staff (Ref. 4)	Analysis and assessment of MLAA programs, FY 1971-80.
RML	NLM staff	Evaluation and management decision leading to more efficient operation of RML network.
Resource	NLM staff	Evaluation of the medical library resource project grant program.

Planned Evaluation Studies

Program	Objective
Training	Evaluation of the experimental medical librarian management intern training program.
Resource	Evaluation of the cost and benefits of health science library consortia.

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*Reference number refers to Documentation section.

CLINICAL CENTER

Accomplishments in Past Year

The number one priority of the 1976 Easton Conference was the establishment of a Medical Intensive Care Unit (MICU) in the Clinical Center (CC). During the past year, the MICU was activated. It has materially enhanced the quality of patient care for critically ill patients, and it has enabled the Institutes to more efficiently use the beds on their units (e.g., by allowing both beds in a two-bed room to be used, since severely ill patients previously requiring single rooms were transferred to the MICU). The MICU is also providing invaluable learning tools and techniques which are being applied to patient care throughout the hospital.

The Medical Information System (MIS) was fully implemented during the past year with the clinical laboratory linking to the system. The MIS is a hospital-wide system which processes medical orders from 28 inpatient units and 12 outpatient clinics. Without a medical information system, the task of processing orders arising from complex protocols would be overwhelming even if staff increases were granted for manual processing. We now know that manual tasks would require many man-hours to achieve a level of service far below that being achieved by the MIS.

Through the combined efforts of CC, DCRT, and Medical Staff representatives, a process for increasing the utility of the medical records while decreasing the physical bulk was implemented for clinical pathology cumulative laboratory summaries. The new report scheme uses the laser-printed technology to array test results by date in an easy-to-follow format. Week-by-week reports are replaced by one compressed summary, making the laboratory report section of the chart quite compact while placing data in a form that makes tracking of results and identification of abnormals quite easy. A cumulative normal values table is part of the report scheme and provides a unique clinical reference for the researcher. With the laboratory reporting scheme as a model, the Medical Record Improvement Committee is pursuing further streamlining related to nursing record, doctor's orders, and other documents.

Although service to Institute programs remains the raison d'être for Clinical Center departments, each department carries out collaborative and goal-oriented research. Notable accomplishments are: (1) definitions of non-A, non-B hepatitis and the start of a clinical trial to reduce the incidence of this disease, (2) the demonstration of the utility of neocytes (young red blood cells) for transfusion to patients with potential iron overload problems and the development of a simplified technique for obtaining neocytes,

(3) exploration and analysis of the nature of the clotting defect in von Eillebrand's disease, and (4) development of a new intravenous contrast material to give sharper definition of hepatic metastases.

A bioethics program has been integrated into Clinical Center activities. Conferences and training sessions in biomedical ethics have been established, individuals at pre- and post-doctoral levels have received training, and consultations for difficult problems in research protocols and patient management have been given.

Summary of Plans FY 1982-1983

During the 1982 and 1983 fiscal years, the Ambulatory Care Research Facility (ACRF) will be fully occupied and operational. In the existing Clinical Center the modernization program, by now in its fifth year, will involve upgrading of selected nursing units, renovation of the Pharmacy, construction of the Medical Intensive Care Unit, and a number of other projects. Present outpatient visits of 100,000 per year are expected to increase to 150,000, while the inpatient levels will remain essentially unchanged at 75 percent occupancy, or 380 patients per day. The hospital will have more of the characteristics of a 24-hour, seven-day-a-week hospital by expansion of intensive care; responsibility for plasmapheresis and leukopheresis; operation of a central facility for inpatient and outpatient electrocardiography, pulmonary function testing, echocardiography, and other functions; and operation of some inter-Institute programs such as genetics. The Medical Information System (MIS) will be processing orders from 12 outpatient clinics and 28 inpatient units at a speed and accuracy not possible by manual processes. The MIS, by enabling the Clinical Center to maximize the use of research data bases, will be providing clinical investigators with information not available in previous years. The primary task of the Clinical Center will continue to be timely and effective provision of services to the clinical programs. The operation of the ACRF, disruptions caused by the modernization projects, shifts in patterns of research, and increased demands will pose many management challenges which can be met, assuming adequate staffing and funding.

Initiatives

The initiatives for the Clinical Center in 1982 and 1983 are:

The Hospital. Prestigious outside groups in their reviews of Radiology, Clinical Pathology, Nursing, Nutrition, and other services, have strongly recommended that the Clinical Center serve as a role model for the hospital community nationwide. With the modernization of the Clinical Center, including the ACRF, the Clinical Center, in their viewpoint, can take its place among the very best of modern hospitals and once again become a standard bearer. With the availability of state-of-the-art equipment and processes, coupled with a highly professional research-oriented staff, new and original approaches in hospital diagnostic services and therapeutic techniques are probable.

One model of the sort of contribution that can be made by the Clinical Center is the Medical Information System (MIS) that we are now evaluating. This system, modified to meet the needs of a research hospital, is expected to be used by university teaching hospitals and possibly by military and Veterans Administration hospitals. Without doubt, the MIS, as modified here, is the most sophisticated and advanced medical information system extant in terms of the numbers and kinds of patient care information processed.

Another area of interest where the Clinical Center is testing new hospital techniques is the program of total care, which will be fully implemented by 1983. This provides for continuity of care of patients by physicians and nurses, regardless of the patients' inpatient or outpatient status. Based on a shared knowledge of the research protocol, a patient would be followed by a physician-nurse team, whether the patient were in a bed or in a clinic. Administrative coordinators would assist in this effort. This approach is of considerable interest to other hospitals and may serve as a model for integration of patient care sites.

Research. All of the ad hoc advisory groups that have reviewed our departments have recommended that Clinical Center departments should be engaged in research to improve their respective missions. As some of the space constraints are removed with the opening of the ACRF and with the purchase of new equipment, we see the opportunity to expand that type of collaborative research with Institute scientists that has already proved so fruitful. Some of the specific areas where one may predict significant progress are new pheresis techniques, computer-assisted scintigraphy for evaluation of pulmonary function, real-time ultrasonography, definition of the usefulness of second generation CAT scanners, exploitation of positron-emission tomography, laboratory automation, and computerization of intensive care unit (ICU) techniques.

Education. With the availability of teaching space in the ACRF (amphitheater, etc.), the Clinical Center education programs will be greatly facilitated. NIH will increase its leadership role for training the medical subspecialties and related research areas. Further active participation by universities may be expected. Examples of programs to be undertaken (some are now under way in a modest way) are as follows:

- Education to support the research mission.
- Coordination and strengthening of existing inter-Institute educational programs (endocrinology, clinical pharmacology, genetics, immunology, and computer sciences) and development of new integrated training programs.
- The provision of continuing medical education to satisfy professional requirements.
- Minority training in clinical investigation.

Bed Utilization

Statement of Issue

Bed utilization in the Clinical Center can be improved. On a typical day, a certain number of beds are vacant, and yet some programs (National Cancer Institute and National Institute of Mental Health) could use additional beds. This is a result of the rigid bed allocations to the Institutes which have remained essentially unchanged since 1957.

Problems and Implications

Pressures and needs for beds fluctuate each year, but the pressure from NCI remains constant. In responding to these pressures, the important constraint on the Clinical Center, apart from the bed allocation, is the necessity to maintain a nursing force, trained in a variety of subspecialties, at sufficient strength to cover maximum bed utilization. We do not have the positions to do this, nor are we able to predict or manage wide fluctuations in bed utilization.

Alternatives and/or Suggested Position

The 1976 "Report of the Investigation of NIH" prepared by the House Subcommittee on Health and the Environment recommended that "the allocation of beds in the Clinical Center be critically evaluated and appropriate reallocation be made as rapidly as possible." The Clinical Center has also suggested alternatives such as providing the Director, CC, with the authority to utilize vacant beds in certain selected nursing units. Additionally, we have prepared major reorganization plans that would eliminate some Institute prerogatives for ward autonomy. The necessity to construct a six-bed unit for the National Institute on Aging will also necessitate some decision about bed redistribution.

Outpatient Program Implications

Statement of Issue

Implications of an expanding outpatient program for the Washington area medical community.

Discussion of Issue

- Competition for patients.
- Inadequate referral of patients.
- Possible resentment of NIH as outpatient programs expand.

Suggested Position

- Use outpatient clinics for continued medical education of area physicians.
- Develop clinical appointments for area physicians who wish to work in clinics.
- Use area medical students in outpatient clinics.

DIVISION OF RESEARCH SERVICES

Summary of Accomplishments During FY 1980

The Division of Research Services (DRS) comprises four branches: Biomedical Engineering and Instrumentation (BEIB), Library (LB), Medical Arts and Photography (MAPB), and Veterinary Resources (VRB). During FY 1980 the DRS staff continued to increase overall services provided to the NIH community even though resources remained at the FY 1979 level.

In FY 1980 DRS provided NIH investigators with: 11,000 instrumentation and engineering projects, 58,000 library loans, 137,000 library photocopies, 27,000 illustrations, 237,000 photographs, and 1,000,000 defined laboratory animals. In addition, DRS controlled an outbreak of ectromelia, which was introduced into an Institute's mouse colony and threatened similar colonies throughout NIH.

The DRS has continued to exert leadership in developing new and more cost-effective research support activities which can benefit the entire biomedical community. Examples include:

- A program to breed captive chimpanzees in the United States, resulting in a self-sustaining population to meet the needs of biomedical research.
- A centralized microanalytic facility, available to all NIH intramural scientists and providing equipment and professional staff, which would be too costly for individual laboratories to maintain.
- The operation of a Scientific Equipment Rental Program, which increases the efficiency and reduces the cost of NIH research.
- A program to "bank" NIH genetic resource stocks and strains through embryo cryopreservation.

The Division's capabilities to meet the needs of the NIH intramural scientists also benefit the extramural community. For example, the Genetic Resource, which must be maintained to provide animals for NIH intramural research, also serves as a base of breeding animals for several NIH extramural programs. Animals from the breeding nuclei are made available to research institutions throughout the world. During FY 1980, institutions located in 16 countries were provided breeding nuclei from this unique resource. The Interagency Primate Steering Committee has continued the development of programs to ensure an adequate supply of primates for the Nation's biomedical research programs. A contract was established with the World Health Organization which will help to ensure the development of an international primate supply program. The Division's engineering capabilities have served as an important element in the development of a cooperative training program to improve instrumentation for research and medical application in Egypt. A similar program is currently being developed for Venezuela.

The professional DRS staff, as a part of its mission, actively participated in the NIH intramural research program and authored or co-authored 65 scientific publications.

Summary Plans for FY 1982-83

For FY 1982 and FY 1983 the Division of Research Services will continue providing NIH intramural scientists with a wide range of high-quality products and services required in modern sophisticated research. These include a variety of library services, including bibliographic searches and translations, the application of physical science technology to the solution of biomedical problems, the provision of research animals and facilities, and furnishing an array of medical arts and photographic services. These services will be enhanced by selectively adding new activities and improving existing programs.

Maintenance of a sperm bank for animal models of human disease will continue. Techniques for the cryopreservation of embryos from approximately 150 stocks and strains of the Genetic Resource will be improved, with efforts to enhance the reproductive performance of laboratory animals. Behavioral, nutritional, and reproductive studies will be expanded so as to produce better defined laboratory animals for specific research requirements. Studies to develop new animal models of human disease will be reinforced, and efforts to provide more specific genetic characterization will be intensified. Monitoring of animals for conformance to genetic and microbiologic standards will be strengthened through development of new procedures.

For the first time, the Division will be able to offer a centralized research rodent-holding service in FY 1982. This will be enabled by the renovation of Building 14B in FY 1981. Designs for renovating Building 14F to provide additional barrier facilities for rodents will be completed, with construction anticipated in FY 1983. Facilities at the NIH Animal Center will be upgraded to provide for the more efficient production of dogs, improve the health quality of goats, and provide shelter for expensive farm machinery.

Programs of the World Health Organization and the Pan American Health Organization will be monitored, and assistance given in developing and implementing an International Primate Supply Program through improved breeding and conservation.

Computerized programs for the maintenance of animal inventory and billing systems are planned for implementation. It is proposed to award a contract for the development of a comprehensive computer program and to install and maintain the required equipment to assist in managing rodent colonies of the Genetic Resource.

By FY 1982 an automated library system will be implemented providing a data base reflecting the Library's complete holdings and label machine recognition for the collection. The new computerized system will permit Library staff to monitor and analyze the contents of the Library's collection and conduct studies of acquisition patterns and trends. An online automated circulation control system will be installed with implementation scheduled for FY 1983. This system will be used to provide for charging and discharging books, renewing charges, reserving materials, clearance checks for employees leaving NIH, and statistical reports.

A microfiche printing system will be implemented in FY 1982 to replace the present system for producing photocopies. The Library's entire monograph and journal holdings will be converted to a machine-readable mode, which is a prerequisite for an automated system. The publication Current and Non-Current Journals will be updated.

The Library community is converting its cataloging records to the second revision of the Anglo-American Cataloging Rules. In order for the NIH Library to remain compatible and in communication with its peers, policies for the conversion will be developed and implemented.

Computer graphics capabilities will be available in-house with a compatible contract backup. New equipment will be purchased to widen the spectrum of magnification in fluorescent microscopy and to allow multiple camera filming of extended surgical and scientific procedures.

The microanalytic facility will be expanded in two directions to respond to the expressed needs of the NIH investigators. The existing electron microprobe and electron energy loss spectrometer capabilities are being extended. The image processing capability will allow electron micrographic pictures to show the distribution of biologically important elements. In addition, a novel mass spectrometric facility is being assembled to explore more efficient ion sources (secondary ionization mass spectrometry), which should enable the measurements of molecular weights and structural subgroups of minute amounts of biologically important molecules.

Development of a nuclear magnetic resonance imaging system has reached a stage where it will be possible to begin to examine animals and human subjects. This tool should be especially valuable for the diagnosis of pathologic conditions such as hydrocephaly in neonates.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Director's Overview

The challenge facing the Division and the NIH is to maintain continuity and to increase sophistication in computing in the face of constant change. Biomedical research is always exploring new fields and developing new investigational techniques. Computer science and computer technology are also dynamic, constantly producing new mathematical techniques, improved machines, and computer software techniques.

Information processing has an inescapable significance in addressing the Nation's health problems. It is a function integral to all NIH biomedical research program activities: patient care, health science administration, and program direction.

The assigned goal of the Division of Computer Research and Technology (DCRT) is nothing less than ensuring that the computer, a preeminent information processing tool, is in its several forms broadly useful across all these NIH activities.

The nature of this assignment requires DCRT to pursue a strategy that incorporates a remarkable spectrum of scientific and technical expertise into an integrated set of functional activities that maximize, across changing time boundaries, its contribution to NIH biomedical research programs.

In simpler words, DCRT as part of the core of NIH activities must use its limited resources to cover a large range of computer needs at NIH in a way that brings all the pieces together effectively.

FY 1981

Due to resource constraints DCRT will be hard pressed to continue collaborative and service-oriented efforts at our current levels. Several positive events in FY 1981 defined more clearly the path along which NIH can best respond to the challenge through FY 1983-85.

As a result of the contracts awarded in FY 1981 for the DEC-10 and IBM systems, the capability exists for expansion and modification of the systems to meet NIH needs and to keep up with the ever-changing state-of-the-art in the computer industry. Due to the ability to rapidly expand capacity under the new contractual arrangements, we can now continue to link additional mini- and mid-size computers to the central facility. This step will bring the power of the central facility more directly into the laboratory and clinic and allow the scientist and clinician to have access to numerous services for rapid and efficient processing of their data.

Another major segment exploits advances in small computing devices linked closely to the laboratory or clinic. Here the thrust of developments in Very Large Scale Integrated electronic circuitry makes it clear that a great deal more can be accomplished.

The manufacturers of computer hardware, by using technological advances, are able to provide far more sophisticated central processors at much lower cost/performance ratios than in the past. The general area of image display and processing is a good example. A few years ago, image work (because of the huge number of data points that make up even a modest picture) was limited to very large and expensive installations. Today, the Computer Systems Laboratory (CSL) is able to set up the tools for image analysis by employing computers that would have been completely out of reach just a short time ago. CSL engineers and scientists are in fact now planning for an image processing facility including a virtual memory computer and several high-quality displays. If the funding request is approved in 1981, this facility will be installed for use by scientists throughout the NIH community whose work can be aided by image analysis techniques.

The limitation on progress is no longer the ability to create reliable computer hardware. The limitation is now the ability of competent people to exploit the potential of that hardware. NIH currently, and perhaps through FY 1985, will be severely disadvantaged in recruiting and hiring in an extremely competitive national and international market for computer scientists and digital engineers.

FY 1982 Program Changes

Despite anticipated resource constraints in 1982, we will endeavor to maintain a stable base of support for the NIH programs. Projects will cover such areas as:

- Development of specialized mathematical methods of representing the microcirculation of perfused organs.
- Development and improvement of mathematical methods and numerical algorithms for the solution of partial differential and other nonlinear equations.
- Comparative study of multivariate and univariate models in the analysis of biochemical time series.
- Further implementation of an image processing facility for scientists whose work can be aided by image analysis techniques.

- Continuing implementation efforts on the NIH Material Management System and Financial Management System, to bring closer the planned integrated NIH Administrative Data Base.

- Continuing NMR (nuclear magnetic resonance) investigations on the conformation of angiotensin, bleomycin, and bradykinin.

- Application of scintigraphic techniques to the diagnosis and monitoring of renal hypertension, proceeding through additional studies in animal models to eventual use in patients.

- If the image processing project is funded in 1981, additional efforts will be directed to further developing that system to enhance its benefits to the research community.

FY 1983 Program Changes

No significant changes will occur in FY 1983 over FY 1982 if the image processing project is funded in FY 1981. Ongoing efforts will continue at a static pace for the types of projects listed in FY 1982. However, if the proposed image processing project is not funded until FY 1983, intensive efforts will have to be mounted to attempt to make up the lost ground during the past two fiscal years. It is difficult to assess the state-of-the-art at that point in time, but new developments in electronic circuitry telecommunications and other information processing techniques would influence the direction in which the Division's programs should move. These decisions would be influenced by research developments in the areas of biology, biochemistry, medicine, and genetic engineering.

DIVISION OF RESEARCH GRANTS

Accomplishments for Calendar Year 1980

The Division of Research Grants (DRG) centrally receives all PHS applications for research and research training support and makes referrals to PHS components; assigns NIH applications to appropriate Bureau/Institute/Divisions (BIDs) and DRG initial review groups (IRGs); provides for scientific review of NIH research grants; and collects, stores, retrieves, analyzes, and evaluates data needed in the administration of extramural programs.

Some of the Division's recent accomplishments include:

- Processed 27,218 Public Health Service competing applications, 19,465 noncompeting applications, and 2,229 interim supplements during calendar year 1980. Of the 27,218 applications, 20,046 were assigned to DRG for review.

- Prepared and extensively revised materials for orientation of staff and scientific review groups, such as Handbook for Grants Assistants, Handbook for Executive Secretaries, Orientation Handbook for Members of Scientific Review Groups and Project Control Handbook, and an extensive slide collection on the peer review process and NIH Review of Research Grant Applications (booklet to accompany slide presentations); actively participated in the publication of NIH Extramural Programs (which replaced the Guide to NIH Programs and Awards).

- Began revision of Handbook of Referral Officers and prepared "Referral Office Brochure."

- Completed and distributed extensively revised PHS Form 398, "Research Grant Applications," and PHS Form 416-1, "Postdoctoral Fellowship Application"; and instituted new procedures to store collected information on the new PHS Form 398 to ensure greater confidentiality of data.

- Received charters for five new study sections and one revised charter for a "flexible" study section; justified and began clearance process for three new fellowship study section charters also in a flexible mode.

- Revised review process of fellowship applications and applications in response to RFPs (request for applications) to shorten review time to address continued heavy workload.

- Conducted four meetings involving the chairpersons of all NIH scientific review groups and prepared the Proceedings of the 1979 Meeting of the Chairpersons of NIH Scientific Review Groups.

- Developed a model central service unit within DRG including a paper processing center, a microfilm center, and a word processing center to streamline the flow and processing of paper.

- Processed about 20,000 queries through the IMPAC* system during calendar year 1980, and 1,368 requests for information through the CRISP** system.

- Provided the Office of the Director, NIH, statistical support for budget forecasting and development.

- Following the decision to discontinue use of normalized scores, developed a new system for the presentation and use of scores in collaboration with BID staff.

- Introduced computer graphics technology in the preparation and distribution of reports to facilitate the comparison of priority scores and recommendation rates.

- Introduced computer technology and streamlined procedures for greater economy in the maintenance and operation of the CRISP system.

- Designed an interactive query system for the NIH Committee Management Information System.

- Developed a new computer-based report program to reconcile the IMPAC and NIH central accounting systems.

- Continued special analyses on long-term trend data on principal investigators on research grants.

Program Plans for FY 1983

Some of the plans and management actions the Division will undertake include the following:

- Reorganization of several components of DRG to strengthen management.

- Continued effort toward improving the management of workload by better use of space and equipment and the development of training programs for employees.

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* Information for Management Planning, Analysis, and Coordination.

** Computer Retrieval of Information on Scientific Projects.

- Planning for chairpersons' meetings and publication of the proceedings of those meetings.

- Extension of utilization of central service unit concept and related new technology.

- Revise charters of selected existing study sections into a flexible mode.

- Expand the variety and scope of certain extramural data available in hard copy or microfiche to improve our ability to respond to requests without new programming.

- Continue effort to improve our knowledge and utilization of all Division of Computer Resources and Technology systems that are applicable to our reporting work.

- Acquisition of new technology to improve the control, turnaround time, and responsiveness of our reporting and analysis.

- Improve documentation of the capabilities, contents, and principles of the IMPAC system--specifically information sources, data limitations, and reporting concepts--to upgrade staff knowledge and performance.

- Preparation of a system to facilitate and decentralize production of several important management documents to the BIDs, such as the "Notice of Grant Award."

- Preparation for implementation of the new Department accounting network.

- Implement alternative systems to replace the IMPAC abbreviated files to facilitate access and shorten report processing time.

- Dissemination of information on the content, structure, function, and use of the CRISP system--including BID direct access methods.

- Development of an interactive search system for CRISP.

- Development of interactive data capture to record initial review group action.

- Development of an interactive system to record data and prepare special reports required by the Office of the Director pertaining to NRSA* programs.

- Improvement of BID access to data in the grant applicant file, the summary training file, and the computerized file for the NIH inventory of clinical trials.

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* National Research Service Awards

- Completion of Handbook for Referral Officers and updating of (1) Handbook for Grants Assistants, (2) Handbook for Executive Secretaries, (3) Orientation Handbook for Members of Scientific Review Groups, and (4) slide collection on peer review with accompanying booklet.

Application Workload

Statement of Issue

Continued high workload in number of applications submitted to NIH for referral and review by DRG.

Discussion of Issue

The Division continues to have an extremely high workload. In calendar year 1980, the Division processed 27,218 Public Health Service competing applications, 19,465 noncompeting applications, and 2,229 interim supplements. Numbers of applications are as high or higher in FY 1981.

DRG management has utilized new technology, systems, and management techniques to keep pace with the heavy requirements. The Division has no control over the numbers of applications submitted but remains committed to maintaining quality in the receipt, referral, and review of applications and statistical data management. To do this, DRG will need full support in FY 1982 and FY 1983 to hire appropriate staff, purchase necessary equipment, and utilize space in an optimal manner.

We began in March 1981 a concentrated review of our operations in receipt, review, and data management, and have developed a broad range of procedures and policy recommendations, many of which will need extensive further discussion throughout NIH before possible implementation. Acceptance and implementation of new systems to manage our workload in an era of scarce resources will represent a major cluster of activities in FY 1982 and FY 1983 for the Division.

Section Three

TRANS-NIH HEALTH PROBLEMS

Many areas of scientific investigation extend beyond the interests of the individual Institutes or are not easily placed within one categorical Institute. Trans-NIH coordinating committees have been used since 1977 as a structured method for devising proper research strategies in fields that are not restricted to the purview of individual Institutes. The committees track research and the support for research in their field of study and advise administrators on the selection of areas for research emphasis, joint program announcements and awards, and research centers. The committees also sponsor symposia and workshops and endeavor to ensure coordination of efforts within NIH and cooperation with agencies outside NIH.

During FY 1980, there were seven active trans-NIH programs: Arthritis, Cystic Fibrosis, Diabetes, Nutrition Research, Epidemiology, Research Training and Manpower Development, and the National Toxicology Program.

The following section provides brief summaries of selected plans, accomplishments, and issues of concern in a given activity area. Each summary is followed by a review prepared by the chairperson of the relevant trans-NIH committee or by some other individual with primary responsibility for a particular trans-NIH program area.

TRANS-NIH COORDINATING COMMITTEE ON ARTHRITIS

Summary of Plans, Accomplishments, and Issues

Plans for Fiscal Years 1982 and 1983

- A conference on immunogenetics and infectious agents vis-a-vis the etiology of rheumatic disease will be held.
- A conference on immune complexes found in low concentrations in diseases of concern will be held.
- The Committee will evaluate research on collagen to judge the efficiency of current research support.
- The Committee will encourage research in exercise pathology and will support further research on artificial joints.

Selected Accomplishments

- An Arthritis Epidemiology Conference was held (first since 1966) to review current knowledge, identify gaps, and suggest research opportunities. An annotated bibliography of research since 1966 was prepared prior to the conference and proceedings will be published.
- The NIH, the American Academy of Orthopedic Surgeons, and the Orthopedic Research Society cosponsored an international, interdisciplinary "Workshop on Idiopathic Low Back Pain." Five panels constructed lists of research recommendations with statements of feasibility. A summary and proceedings will be published.
- A workshop on "Heritable Connective Tissue Diseases" was held, with emphasis on molecular genetics and basic biochemical defects as the areas of emphasis.
- Liaison was established with the newly organized National Institute of Handicapped Research (NIHR). The rheumatologic community has recommended research initiatives to the NIHR.
- An informal interagency orthopedic biomechanics group has been organized involving the National Institute of General Medical Sciences (NIGMS), Veterans Administration (VA), Food and Drug Administration

(FDA), National Aeronautics and Space Administration (NASA), NIHR, and the National Bureau of Standards (NBS).

Issues

There has been Congressional interest regarding the NIH position on research with dimethyl sulfoxide (DMSO) and the status of clinical studies employing DMSO. A two- to three-year clinical trial has been initiated on the efficacy and safety of DMSO in treating digital ulcers of scleroderma.

Areas of Congressional interest which are being emphasized by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) are arthritis in children, epidemiology of rheumatic diseases, and exercise pathophysiology and sports medicine.

REVIEW OF PLANS, ACCOMPLISHMENTS, AND ISSUES

Accomplishments

The Arthritis Epidemiology Conference, the first such meeting since 1966, was held at NIH on September 24-26, 1980, to focus attention on and attract researchers to epidemiologic studies on rheumatic diseases. An interdisciplinary group of 48 academic rheumatologists and senior epidemiologists reviewed the current state of epidemiologic knowledge of several rheumatic diseases, identified gaps in such knowledge, and suggested research opportunities. An annotated bibliography on "Epidemiologic Studies of the Rheumatic Diseases," covering the literature since 1966, had been prepared prior to the conference to aid the conference participants and to serve as a published resource for future researchers. The conference proceedings will also be published. Highlights of the conference include:

- "Epidemic polyarthritis," caused by Ross River Virus, was isolated from over 100 patients during a recent epidemic in the South Pacific;
- "Lyme arthritis" was recently identified at sites outside of New England, the tick vector was identified, a need was recognized to search for the offending microorganism, and preliminary data indicate that early penicillin therapy decreases frequency of late sequelae;
- A prospective study was indicated of asymptomatic persons with HLA-B27 genetic marker to identify environmental factors, e.g., bacteria, causing ankylosing spondylitis and related disorders;
- It was noted that little yield is to be expected from further population studies of rheumatoid arthritis;
- Studies of males with systemic lupus erythematosus were encouraged to identify etiologic factors;
- Population studies of osteoarthritis were indicated to identify risk factors, which may be multiple;
- A need was identified for discussion of the epidemiology of disability and the development of validated instruments to do so; and
- Several data resources for epidemiologic studies were reviewed.

An international, interdisciplinary Workshop on Idiopathic Low Back Pain was held in Miami on December 8-10, 1980, cosponsored by the NIH (NIADDK), American Academy of Orthopedic Surgeons, and Orthopedic Research Society, with significant participation by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the National Institute of Dental Research (NIDR). The workshop brought together scientists of virtually all relevant research disciplines (anatomy, pathology, radiology, biomechanics, occupational medicine, neurology, biochemistry, biophysics, orthopedics, neurosurgery, psychology, and epidemiology) to discuss knowns, unknowns, and research opportunities. Five panels constructed lists of research recommendations with statements of feasibility. A summary of the workshop will be published in six months, and the complete proceedings published in one year. "Impairment of back and spine" is the leading cause of limitation of activity among young adults (18-44 years of age) in the United States. The FY 1981 report of the House Appropriations Committee includes a "mandate" for research in this area.

On May 20-21, 1980, a workshop was held on Heritable Connective Tissue Diseases, with special emphasis on osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan's syndrome. Presentations were concerned principally with molecular genetics and basic biochemical defects. Clinical management was also discussed.

The Musculoskeletal Diseases Program Director (NIADDK) has organized an informal interagency orthopedic biomechanics group, including representatives from the NIGMS, VA, FDA, National Academy of Sciences (NAS), NASA, National Institute for Handicapped Research (NIHR), and National Bureau of Standards (NBS).

Liaison with newly established NIHR was effected by inviting its Director to participate in the Arthritis Interagency Coordinating Committee (AICC) and by other means. At the July meeting of AICC, there was a full discussion of the broad and diverse mandates of the Institute. In subsequent meetings at NIHR, suggestions for research by NIHR from the rheumatologic community were solicited. Recommendations have been formulated by a group (assembled by the Arthritis Foundation) with the Chief of Rehabilitation at the Clinical Center (NIH) playing a leading role; these recommendations to NIHR emphasize the importance of developing reliable methods of assessing functional status of persons with rheumatic disease, and investigating the efficacy and safety of nonpharmacologic treatments (heat, cold, diathermy, ultrasound, etc.). Further, NIH has considerable investment in research on inflammation and pharmacologic management of rheumatic diseases, and these need not be repeated by NIHR.

The Data Systems Subcommittee of the AICC has discussed progress in ARAMIS (American Rheumatism Association Medical Information Systems) and plans for future HANES (Health and Nutrition Examination Survey) surveys by the National Center for Health Statistics (NCHS). Detailed plans for re-survey of HANES I are being developed.

The Office of Health Information and Health Promotion cited the Arthritis Information Clearinghouse as "model entry" among 76 national clearinghouses.

Plans for FY 1982 and FY 1983

- Conference on immunogenetics and infectious agents, bacterial and viral, in etiology of rheumatic diseases. Striking associations of

HLA-B27 and "Public Antigen" have been established for ankylosing spondylitis, Reiter's syndrome, and related diseases. Current evidence suggests pathogenetic roles for Shigella, Klebsiella, and Yersinia infections. Antigens in the HLA-D locus and B-cell alloantigens (HLA-DR) are significantly associated with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and juvenile arthritis with iritis. Diphtheroids and EB virus have been associated with rheumatoid disease.

- Conference on biologic and pathogenetic significance in immune complexes, found in low concentrations in diseases such as systemic lupus erythematosus, rheumatoid disease, and various forms of arteritis.

- AICC is planning to analyze research on collagen supported by both extramural and intramural programs of several Institutes at NIH to evaluate the efficiency of current support in this area.

- There is need for research in exercise pathophysiology. Increasing numbers of Americans are engaging in sports activities and physical fitness programs. Few highly meritorious scientific investigations are being generated to study positive and negative effects of such activities in various segments of the population. Studies on mechanisms of musculoskeletal injury and repair are few. A workshop is planned for FY 1982 on sports activity and injury to the knee. Report of FY 1981 House Appropriations Committee identified sports medicine as an area to be encouraged by the NIADDK's Musculoskeletal Diseases Program.

- Continuing support for research on artificial joints is clearly warranted. The number of both initial and revision operations for joint replacement remains high. Although the early success rate is impressive, there is great need to improve long-term prognosis. Research areas of importance include surface replacements, bone ingrowth technology, durable materials, and biocompatability. An NIH Consensus Conference on Total Hip Replacements will be held in FY 1982. Also planned for FY 1982 is a workshop on interface phenomena.

Issues

There has been an increasing interest in support for research on arthritis in children, both in Congress and within the Arthritis Foundation, which formed a new section--the American Juvenile Arthritis Association. Research in juvenile arthritis is at a low level, and worthy applications are sought for both research grants and training.

There is continuing interest in epidemiologic research within the National Arthritis and Advisory Board, which has been reauthorized, and the Arthritis Foundation.

Legislation concerning DMSO may be reintroduced, and there is new Congressional interest in sports medicine.

TRANS-NIH CYSTIC FIBROSIS COMMITTEE

Summary of Plans, Accomplishments, and Issues

Plans for Fiscal Years 1982 and 1983

The Committee plans to observe trends in grant applications and in approved grant-supported projects to evaluate the effect that publicity measures of the last two years have had in stimulating research proposals in this area.

The Committee will stay abreast of scientific developments and be prepared to intervene if an activist role taken by NIH would be beneficial.

Selected Accomplishments

The Committee is closely monitoring the response to the joint program announcement, published cooperatively by six Institutes, which solicited grant applications for studies relevant to cystic fibrosis.

Issue

A question may arise regarding why NIH is not assuming a more active posture in this area. Because cystic fibrosis is a genetic disease, the likelihood of cure is exceedingly small, and major new advances based on essentially palliative approaches are not to be expected. All further approaches depend on identifying the abnormal gene product and defining its biochemical structure and function. Since there are no clearly apparent leads in this field at present, the most promising approach is to encourage investigator-initiated proposals from as wide a segment of the scientific community as possible.

Trans-NIH Cystic Fibrosis Committee

REVIEW OF ACCOMPLISHMENTS, PLANS, AND ISSUES

Accomplishments

The NIH Cystic Fibrosis Coordinating Committee was heavily engaged during the years 1978 and 1979 in cooperating with the Cystic Fibrosis Foundation on the study leading to the report "CF: State of the Art and Directions for Future Research Efforts," and in measures to publicize the report and its findings. Two chapters of the report were reprinted and distributed widely to grantee and contractor organizations, and, with the assistance of the Cystic Fibrosis Foundation, a small flier calling attention to research needs in cystic fibrosis was printed and broadcast. In addition, the six Institutes with scientific concerns germane to cystic fibrosis cooperated in publishing a program announcement soliciting grant applications for studies relevant to cystic fibrosis.

The beliefs underlying the above approach were primarily these:

- As a genetic disease, cystic fibrosis is not likely to be curable. Although much has been accomplished to extend the life span of cystic fibrosis victims by treatment of secondary manifestations, the situation is still unsatisfactory, and major new advances based on essentially palliative approaches are not to be expected.

- Screening, genetic counseling, early diagnosis, and conceivably an approach to treatment based on bypassing or overcoming the genetic defect, all depend on identifying the abnormal gene product and defining its structure and function in biochemical terms. There being no clear apparent lead that is scientifically ripe for exploitation, the most promising approach to this discovery is to encourage investigator-initiated proposals from as wide a segment of the scientific community as possible.

Plans for Fiscal Years 1982 and 1983

The Committee plans to:

- Attempt to measure the time trend of cystic fibrosis-related grant applications and approved grant-supported projects. An upward trend will suggest that the publicity measures of the last two years have had an effect. Even more convincing will be evidence that scientists who never before proposed to study cystic fibrosis are entering the field.

- Maintain contact with scientific developments in the field and be prepared to intervene if scientific opportunities develop, which may not be properly exploited in the absence of an activist role for NIH.

TRANS-NIH DIABETES COORDINATING COMMITTEE

Summary of Plans, Accomplishments, and Issues

Plans for Fiscal Years 1982 and 1983

- Studies will be encouraged on the complications of diabetes: cardiovascular, ocular, neurologic, obstetric, and perinatal.
- The further development of investigations of genetic, immunologic, and viral factors in the etiology of diabetes will be promoted.
- Clinical trials will be conducted on (1) the effect of control of blood glucose on complications of diabetes, (2) the effect of early treatment, and (3) the effect of metabolic control on obstetric and perinatal complications of diabetes.
- Education and information programs will be implemented to inform health professionals and the public of the results of the Diabetic Retinopathy Study.

Selected Research Accomplishments

- Demonstration of an association of insulin-dependent diabetes with virus infection in man.
- Production of human insulin, somatostatin, and growth hormone by bacteria using recombinant DNA techniques.
- Elucidation of the mechanisms by which obesity induces diabetes and the biochemical basis through which weight reduction, modification of diet, and exercise improve the diabetic state.
- Demonstration of the therapeutic benefit of laser photocoagulation in preserving vision in the patient with proliferative diabetic retinopathy.
- Demonstration in laboratory animals that pancreatic islets can be transplanted across major histocompatibilty barriers to cure diabetes without immunologic rejection.

- Development of automated preprogrammable insulin delivery instrumentation (pumps) which permits normalization of blood sugar levels in diabetics for prolonged periods.

Issues

The Trans-NIH Diabetes Program was charged by the Director of NIH to serve, through the National Diabetes Information Clearinghouse (NDIC), as the central provider of diabetes-related information and education materials. The Health Service Promotion Act of 1980 (S. 988) assigns this responsibility to the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). This mission is being accomplished, but budgetary constraints will restrict the ability to develop and implement new education and information programs.

Legislation authorizing diabetes research and training centers (DRTC) mandated a geographic distribution. Presently, no centers exist west of St. Louis. A better geographic distribution can be achieved only by a modest expansion.

REVIEW OF ACCOMPLISHMENTS, PLANS, AND ISSUES

Research Accomplishments

Not since the discovery of insulin over half a century ago has the outlook for advances in the treatment, ultimate prevention, and cure of diabetes been as promising as it is today. Significant accomplishments in basic and clinical investigation have provided a practical base for the development of a broad range of therapeutic measures applicable to both the immediate and long-term needs of diabetics. Among these recent research achievements are:

- Significant advances in understanding of gene structure and expression and in recombinant DNA biology which are applicable to a spectrum of diabetes problems ranging from the development of the disease to the unlimited production of human insulin.
- Demonstration of the importance of genetic, viral, and immunological factors in the development of diabetes.
- Better understanding of the fundamental mechanisms involved in insulin synthesis, secretion, and action.
- Identification of the permeability of the blood-retinal barrier as a major factor in the onset of diabetic retinopathy.
- Development of pancreatic islet transplantation techniques which circumvent the phenomenon of immunologic rejection and which correct the diabetic state in animal models.
- Development of insulin infusion systems (open-loop infusion pumps and closed-looped systems, e.g., "artificial pancreas") which normalize elevated blood sugar levels in humans and animals.
- Demonstration in man and animals that normalization of blood sugar levels for short periods of time can improve and correct some of the functional defects of the disease (e.g., perinatal mortality and blood vessel leakage in the eye).
- New insight into the formation of atheromatous lesions and development of hypotheses on how diabetes exacerbates and accelerates this process.
- Documentation of the effectiveness of medical procedures in the treatment of certain long-term complications of the disease, such as anti-hypertension therapy in kidney disease and laser beam photocoagulation in diabetic retinopathy.

Consideration of the impact of these accomplishments on the diabetic's quality of life reemphasizes that continued, vigorous support of diabetes research is critically important.

Trans-NIH Diabetes Coordinating Committee

Plans for Fiscal Years 1982 and 1983

Stimulate and foster basic and clinical research through various programmatic initiatives, such as program announcements, request for applications, interdisciplinary workshops, and the like in the following areas:

- Genetic, immunologic, viral, and other environmental factors in the etiology of diabetes mellitus and its complications.
- Endocrinologic and metabolic aspects of the pathogenesis of diabetes mellitus.
- Immunologic aspects of autoimmune processes that may play a role in the pathogenesis of certain forms of diabetes.
- Diet, nutrition, exercise, and obesity in diabetes mellitus.
- The epidemiology of diabetes mellitus and its complications.
- Transplantation as a potential approach to the treatment of diabetes mellitus and its complications.
- Diabetic nephropathy: etiology, pathogenesis, diagnosis, treatment, and prevention.
- Animal models and their application for research on diabetes mellitus and its complications.
- The cardiovascular complications of diabetes mellitus: etiology, pathogenesis, diagnosis, treatment, and prevention.
- The ocular complications of diabetes mellitus: etiology, pathogenesis, diagnosis, treatment, and prevention.
- The neurologic complications of diabetes mellitus: etiology, pathogenesis, diagnosis, treatment, and prevention.
- The obstetric and perinatal complications of diabetes mellitus: etiology, pathogenesis, diagnosis, treatment, and prevention.
- The behavioral and psychosocial aspects of diabetes mellitus.
- Noninvasive and implantable metabolite sensors for use in diabetes research.
- Application of new biotechnology to research on problems associated with diabetic retinopathy.
- The influence of normal and altered pancreatic functions on the biology, disposition, metabolism, and toxicity of environmental compounds.

- Techniques for the quantitative assessment of peripheral and autonomic nerve function as end points in the evaluation of the effects of long term blood glucose control in diabetes.
- Glucose intolerance and aging.
- Surveillance of 10 to 12 communities to acquire data on several diverse populations to better understand coronary heart disease morbidity in diabetics and nondiabetics.

Implement clinical trials investigating the following:

- The effect of control of blood glucose on complications due to diabetes.
- The effect of early treatment of diabetic retinopathy.
- The effect of metabolic control on obstetric and perinatal complications of diabetes mellitus.

Implement the following education and information transfer activities:

- An information campaign to inform the general public, paraprofessionals, and professionals in the health care field about the results of the Diabetic Retinopathy Study.
- The dissemination of a health care primer outlining standards of treatment for five complications due to diabetes by appropriate Federal agencies concerned with the delivery of health care.
- Analysis, publication, and dissemination of diabetes-related data collected by the National Center of Health Statistics in its Health Interview, and Health and Nutrition Examination Survey (HANES).

Issues

- Diabetes supported research by various BIDs (Bureaus/Institutes/Divisions) has led to significant advances in the treatment of this disorder, including the synthesis of insulin through recombinant DNA technology, the development of automated insulin delivery systems and home blood glucose monitoring techniques which permit better control of the metabolic state than heretofore possible, pancreatic islet transplantation in animals without immunologic rejection, the effective use of photocoagulation of retinal blood vessels to inhibit the progression of diabetic retinopathy and to prevent blindness, and the reduction in perinatal morbidity and mortality in diabetic pregnancies through increased monitoring and surveillance and better control of the diabetic pregnancy.

  In order to take advantage of these significant and major accomplishments, additional research and development is required and additional funding is essential for full utilization of research opportunities.

- Planning and feasibility testing phases of a multicenter clinical trial examining the effect of blood glucose control on complications due to diabetes are expected to occur in winter 1982 and 1983 respectively. Implementation of the full-scale trial is expected in winter 1985.

  The estimated cost of the trial will be $2 million in 1983, rising to approximately $7 to $10 million annually once the full-scale trial is implemented. If NIADDK is to assume the necessary leadership role in this undertaking, resources and specialized personnel above the current levels will be needed.

- One of the charges from the Director, NIH, to the Trans-NIH Diabetes Program was to serve through the National Diabetes Information Clearinghouse as the central resource for providing diabetes-related information and educational materials to scientists, health professionals, diabetics and their families, and to the general public. The recently enacted Health Sciences Promotion Act of 1980 (S. 988) assigns responsibility for communications and education programs to NIADDK. The need for greater attention to education and information transfer was underscored by experts who attended a recent Health Care Delivery Conference sponsored by the National Diabetes Advisory Board (NDAB), which has recommended that the Centers for Disease Control (CDC) take the lead responsibility in this area. While all agree that more attention be devoted to education and information transfer activities, the question remains as to where this function should reside and how much support it should receive.

  Currently, the NIADDK's Diabetes Information Clearinghouse is effectively discharging the information functions assigned to it. It has received many favorable comments from the diabetes community, as well as others, and has reflected well upon the NIADDK and the NIH. NIADDK desires to develop and foster new education and information programs identified by it and the community, but a major new program could only be undertaken at the expense of our support of research.

- The National Diabetes Commission originally recommended the establishment of 15 diabetes centers. Currently, eight centers exist. Additional centers of excellence which could qualify for a DRTC have been identified. The authorizing legislation mandated geographic distribution, but as of now no centers are located west of St. Louis. Evaluation results to date suggest that the centers have been successful in establishing core resources, multidisciplinary research, and greater collaboration. Given these considerations, it seems appropriate to expand the program at a reasonable rate; however, such expansion is prohibited by budgetary considerations.

- The dental complications of diabetes mellitus consist of increased susceptibility to periodontal disease and to oral candidiasis, increased frequency of cleft palate in offspring of diabetic mothers, increased alveolar ridge bone loss in edentulous individuals, and the development of peripheral orofacial neuropathies, including losses in salivation, taste, smell, and mucosal sensory perception. NIDR (National Institute of Dental Research) extramural programs support research on some, but not all, of these complications. Preliminary studies suggest that diabetics have a greater incidence of and more severe periodontal disease because of alterations in the immune system and possible disturbances in collagen metabolism. Since some of the NIDR scientific approaches already initiated seem to offer unusual promise, both in the general field of diabetes and in the area of dental complications, these efforts should be developed further. Of particular interest will be a proposed study on periodontal disease in Pima Indians. This group of individuals has a very high incidence of maturity-onset diabetes and is currently under intense study for other complications of this disease. It is hoped that NIDR will pursue further research in these areas.

- The central issue that concerns the National Institute of Child Health and Human Development (NICHD) about diabetes is the effect of diabetes during pregnancy in fetal mortality and morbidity. The NICHD has taken steps to reduce the excess fetal mortality and morbidity associated with diabetic pregnancies by funding research that addresses this issue. Four of the first five major research programs funded by the NICHD are concerned with study of diabetic pregnancies and with study of infants of diabetic mothers. The continuation of such research is of high priority.

- In October 1979 the NDAB convened over 200 experts to review the current state of the art on research in diabetes mellitus and assess future needs and opportunities. The recommendations of these experts and the NDAB affect all NIH BIDs. The Trans-NIH Diabetes Program, acting through the Diabetes Coordinating Committee, has begun to explore ways in which it can foster the implementation of the recommendations.

TRANS-NIH EPIDEMIOLOGY COMMITTEE

Summary of Plans, Accomplishments, and Issues

Plans for Fiscal Years 1982 and 1983

The Epidemiology Committee will continue present activities and initiate weekly seminars for the epidemiology trainees to familiarize them with epidemiologic studies being performed by all participating agencies.

Selected Accomplishments

The steering committee for the PHS Epidemiology Training Program has completed another annual cycle of recruiting 11 epidemiology trainees from almost 100 applicants.

The Committee has provided four senior epidemiologists to serve as consultants to the National Center for Health Statistics (NCHS) for the development of forms and procedures that will make the National Death Index accessible to bona fide researchers throughout the country.

The Committee has, upon request, provided advice and consultation on legislative matters to NIH's Division of Legislative Analysis (DLA) and the PHS's Office of Health Planning.

Issues

The Paperwork Reduction Act of 1980 provides for systematic reductions in the amount of information the Government may obtain from individuals and institutions. The law does not differentiate information collected for biomedical research from information collected for administrative purposes. Since this is the case, information collection for epidemiological research could be severely constrained, depending upon how OMB administers the law. Every effort should be made to assure an approach which does not jeopardize our ability to conduct this research.

The Committee is concerned that access to medical records could become more difficult or even impractical if legislation is introduced which would prohibit access to medical records without patient consent. Satisfactory legislation in this area was defeated at the close of the 96th Congress . If more restrictive legislation is introduced in this Congress, epidemiologic research could suffer.

Similarly, much useful information is held by Government agencies which cannot, by law, be made available in usable (usually meaning individually identifiable) form, even for legitimate research purposes. Preliminary legislation that HHS drafted, but never introduced into the 96th Congress, would have addressed this problem by providing for exchanges of usable information among closely protected statistical enclaves within Federal departments. An approach must be sought which will permit the revelation of private information to researchers, whose bona fide needs are attested to by an IRB (institutional review board) or similar review, without causing injury to individual subjects by improper disclosure.

Trans-NIH Epidemiology Committee

REVIEW OF ACCOMPLISHMENTS, PLANS, AND ISSUES

Accomplishments

The Committee has held monthly meetings, except during the summer, for informational presentations. Topics covered have included current status of legislation of importance to epidemiologists (medical record privacy, paperwork reduction, etc.), census bureau activities (a proposed post-census national disability survey, and a proposed study linking the 1980 census to the National Death Index), the research potential of the Medicare Statistical System, NINCDS's (National Institute of Neurological and Communicative Disorders and Stroke) data bank on stroke and traumatic coma, the new Philadelphia consortium for clinical trials and other multiclinic studies, NCHS' new Hispanic-American HANES* study, and the NCI's (National Cancer Institute) working group on data resources.

More specific actions have been taken, not by the Committee as a whole, but by working subgroups under its aegis. These should be noted:

- The steering committee for the PHS Epidemiology Training Program, which is comprised of three members from the NIH committee, and one each from the Center for Disease Control (CDC), Food and Drug Administration (FDA), and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), has completed another annual cycle of recruiting epidemiology trainees. This involved national advertising, screening almost 100 applications, and choosing 11 successful applicants through a system of interviews and matches patterned on the NIH's intramural associate program.

- The Committee has provided four senior epidemiologists to serve as consultants to NCHS for the development of forms and procedures that will make the National Death Index accessible to bona fide researchers throughout the country.

- The Committee has, whenever requested, provided advice and consultation on legislative matters to NIH's Division of Legislative Analysis (DLA) and the PHS's Office of Health Planning.

Plans for Fiscal Years 1982 and 1983

These may be summarized as a continuation of present activities related to the exchange of information and as attempting to deal constructively with the issues which are outlined below. One new activity will be the provision of a weekly two-hour seminar/meeting for the epidemiology trainees, beginning in September 1981. These seminars will be instructional in content and will familiarize the trainees with epidemiologic studies being carried on by all cooperating Federal agencies that participate in the program, as well as with the data resources of others, such as NCHS and the Bureau of the Census, which do not.

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* Health and Nutrition Examination Survey.

Issues

"Paperwork Reduction"

The paperwork reduction act of 1980 has become law, and it requires that OMB preside over a 25 percent reduction in the total amount of information the Federal Government collects over the next three years. The law does not differentiate information collected specifically for biomedical research from information collected for the administration of government programs. NIH's research needs might therefore come to be viewed as a "controllable" item in a PHS or HHS budget that is dominated by "uncontrollables" required for the administration of entitlement programs.

If NIH wishes to maintain research activity within its own staff or to be able to attract and retain competent epidemiologic investigators, OMB must be induced to provide an adequate information budget. Money cannot be efficiently spent if research in certain areas is constrained by inability to ask questions of respondents.

Access to Medical Records

Mr. Preyer's Medical Record Privacy bill, which complied with the recommendations of the Privacy Protection Study Commission, would have set forth clear and satisfactory rules governing access to medical records by investigators, but was defeated at the close of the 96th Congress. There is concern that more restrictive legislation, perhaps containing blanket prohibition of data gathering without specific patient consent, may be introduced.

Whereas some types of epidemiologic studies--current cohort studies and case-control studies--can proceed unimpeded by obtaining explicit consent from each subject recruited, other research requires screening large numbers of old medical records to establish historical cohorts to be followed up. Obtaining individual informed consent from each person to whom a record pertains is impractical, not only because of the costs, but because only a fraction of any such population can be located in our mobile society. There are many past examples of important studies which depended on access to old medical records, such as determination of the carcinogenicity of external radiation in the thyroid and the female breast, and evaluation of the risk of cancer in "DES daughters."

If performance of research by government employees and contractors were to be constrained by restrictions on access to information, efficient use of appropriated funds would be impaired, and NIH would produce less useful health-related knowledge per dollar spent.

Access to Other Sources of Information

Much information which could be utilized by epidemiologists, both within and outside the Federal Government, is held by Federal and other governmental agencies which cannot, by law, make it available in usable (usually meaning individually identifiable) form, even for legitimate research purposes.

This problem stems, in part, from our basic political system as a federation of originally sovereign states, in which the powers of the central government are limited by a system of internal divisions. Countries where governmental functions are consolidated to a greater extent at the national level, such as Sweden and Canada, find it much easier to utilize information collected for administrative purposes to support health research as a low-cost by-product.

The Privacy Act of 1974 and the Tax Reform Act of 1976 both discourage the sharing of information among Federal agencies. As a result, information needed for a health follow-up study may have to be collected over again, at considerable expense, and contrary to the objectives of the paperwork reduction initiative. Preliminary draft legislation that HHS was working on, but never introduced into the 96th Congress, would have addressed this problem by providing for exchanges of individually identifiable information among closely protected statistical enclaves within Federal departments. We hope that the new Administration will be interested in pursuing an initiative in this area.

TRANS-NIH NATIONAL TOXICOLOGY PROGRAM

Summary of Plans and Accomplishments

Plans for Fiscal Years 1982 and 1983

Agencies, other than the participating agencies, will be invited to participate more actively in the National Toxicology Program's (NTP) planning and activities concerned with toxicology research, chemical testing, and method development and validation.

The annual Review of Federal Agency Support for Toxicology Related Research will be extended to other Federal agencies involved in toxicology activities. Information from the Environmental Protection Agency (EPA) and the Department of Energy is included in the FY 1981 Review.

Efforts will be made to better define gap areas in environmental toxicology and develop research and testing activities in such areas.

Public dissemination of research, testing, and method development and validation results will be increased and speeded up, e.g., it is planned to publish separate technical reports on results of studies from the prechronic phases of the carcinogenesis bioassay process.

Selected Accomplishments

During FY 1980 the NTP:

- Initiated research to investigate modifying experimental design of the carcinogenesis bioassay to allow resultant data to be more useful for low-dose toxicology evaluation and risk assessment.

- Published the First Annual Report on Carcinogens. The next edition planned for FY 1981 will contain information on up to 100 additional chemicals.

- Completed an international collaborative study of short-term testing methods for carcinogenesis.

- Increased numbers of chemicals being tested in genetic toxicology screen. There were 261 tests completed in FY 1980.

- Broadened protocols in prechronic phases of the carcinogenesis bioassay to measure other toxic effects.

- Formed an NTP Steering Committee to enhance cooperation and information exchange among participating agencies at management and laboratory levels.

- Continued activities in response to current health problems, specifically:

  --Played an active advisory role in the Love Canal problem. Continued testing of 70 of the over 200 chemicals found in this dump site.

  --Took an active role in an interagency group evaluating health effects of Agent Orange. Reproductive assessment studies in male mice have been completed.

  --Continued studies on the chronic toxicology of orally administered asbestos.

REVIEW OF AIMS, ACCOMPLISHMENTS, AND PRIORITIES

Purpose of Program

In November 1978, the Secretary of the Department of Health, Education, and Welfare (now the Department of Health and Human Services [HHS]) announced the establishment of the National Toxicology Program (NTP) as a Department-wide effort to provide needed information about potentially toxic and hazardous chemicals to regulatory and research agencies, and to strengthen the science base in toxicology.

Because many human diseases are known or suspected to be caused by exposure to chemicals, preventing or decreasing human exposure to such chemicals will prevent human disease. NTP aims to develop the scientific information needed to protect the health of the American public from damage by exposure to environmental chemicals.

Program Objectives

Within the framework of its charge to identify those chemicals potentially toxic to humans, the broad goal of the NTP is to coordinate and strengthen the activities of the Department of Health and Human Services in testing chemicals of public health concern, as well as to develop and validate new and better integrated test methods. Four specific goals have been identified:

- To expand the toxicologic profiles of the chemicals nominated, selected, and being tested. In the carcinogenesis bioassay process, a variety of special studies were integrated into prechronic and chronic experiments during FY 1980.

- To increase the rate of chemical testing. The rate of chemical testing for carcinogenesis increased markedly during the first year of the Program, and the rate of testing for mutagenic effects has increased each year.

- To develop, coordinate, and continue to validate a series of tests and protocols more appropriate for regulatory needs. The protocol for the two-year carcinogenesis bioassay has been broadened to include special studies aimed at detecting other types of toxicity during the acute and 90-day testing phases. Test batteries for the assessment of genetic, neurobehavioral, and immunological toxicology have been or are being developed and validated.

- To establish a coordinated communications network to collect, evaluate, and disseminate toxicologic information concerning data compilation, test results, method development and validation, and other program activities. As a complement to the Annual Plan, an NTP Technical Bulletin began publication in FY 1980.

Significant progress toward these objectives has been achieved during the first two years of the NTP.

Progress During FY 1980

The following are brief highlights of important features and accomplishments of the NTP during the past fiscal year:

- Increased numbers of chemicals being tested in genetic toxicology screen. There were 261 tests completed in FY 1980.
- Continued development and implementation of sequential test phases, e.g., mutagenesis testing.
- Broadened protocols in prechronic phases of the carcinogenesis bioassay to measure other toxic effects; about 70 percent of 40 chemical starts in FY 1980 included special studies.
- Expanded activities in the area of reproductive toxicity assessment.
- Continued validation of a comprehensive neurobehavioral test battery.
- Began an interagency coordinated effort on benzidine-based dye mutagenesis, chemical disposition, and carcinogenesis studies.
- Completed an international collaborative study of short-term testing methods for carcinogenesis.
- Changed carcinogenesis bioassay management from prime contractor to chemical manager concept.
- Initiated research to investigate modifying experimental design of the carcinogenesis bioassay to allow resultant data to be more useful for low-dose toxicology evaluation and risk assessment.
- Formed the NTP Board of Scientific Counselors and several working subcommittees of the Board.
- Formed a peer review group for reviewing and evaluating the carcinogenesis bioassay reports.
- Initiated a testing needs study.
- Published the First Annual Report on Carcinogens. The next edition planned for FY 1981 will contain information on up to 100 additional chemicals.
- Initiated a technical bulletin series as well as a literature and management tracking system.

- Completed a systems analysis examination of the research data capture needs of the NTP.

- Computerized and cross-indexed all chemicals listed as under test in the Review of HHS Research Related to Toxicology.

- Formed an NTP Steering Committee to enhance cooperation and information exchange among participating agencies at management and laboratory levels.

- Continued activities in response to current health problems, specifically:

  --Played an active advisory role in the Love Canal problem. Continued testing of 70 of the over 200 chemicals found in this dump site.

  --Took an active role in an interagency group evaluating health effects of Agent Orange. Reproductive assessment studies in male mice have been completed.

  --Continued studies on the chronic toxicology of orally administered asbestos.

Aims and Needs

During the first two years of its existence, the NTP has made significant progress towards its objectives. Yet, much remains to be accomplished. Some of the Program's aims and needs can be highlighted:

- To involve agencies, other than the participating agencies, more actively in NTP planning and activities concerned with toxicology research, chemical testing, and method development and validation.

- To extend the annual Review of Federal Agency Support for Toxicology Related Research to other Federal agencies involved in toxicology activities. Information from the Environmental Protection Agency (EPA) and the Department of Energy is included in the FY 1981 Review.

- To obtain more input from the scientific community into NTP research and testing activities. The FY 1981 NTP Open Meeting was held concurrently with a major toxicology society annual meeting.

- To better define gap areas in environmental toxicology and develop research and testing activities in such areas.

- To increase and speed up public dissemination of research, testing, and method development and validation results, e.g., it is planned to publish separate technical reports on results of studies from the prechronic phases of the carcinogenesis bioassay process.

- To continue joint briefings on chemicals and chemical classes of public health concern, bringing scientists doing the research together with scientists and program officials from regulatory agencies which are in need of specific data to support regulations, e.g., on benzidine-based dyes and phthalates (proposed).

- To improve NTP management tracking systems.

- To develop and evaluate methodology for testing mixtures and combinations of chemicals. This will require extensive input and cooperation from scientists and scientific groups in various agencies and non-governmental organizations.

Establishing Priorities in NTP Research

The development of a program that is equitably responsive to expanded testing, rates of testing, and the development of better test methods requires critical judgment. From a budgetary viewpoint, the segment of the NTP that has the greatest impact on total program capabilities is cancer testing, which with current methods approaches $500,000 per chemical. These modern methods have generally proven to accurately detect chemicals that have carcinogenic potential in humans. These methods, are admittedly crude, slow, and fail to provide data that define major biological factors associated with cancer risk, thereby frustrating the essential process of determining the degree of human risk associated with exposure to a particular chemical. A program must be developed to improve the prevailing systems used for the detection of carcinogenic chemicals, to shorten the path of hazard identification, and to predict risk with a high degree of confidence. Such improvements required in predictive and evaluative detection systems will be bound to the perceptive application of advances in basic research.

The implementation of procedures that broaden the characterization of the toxic properties of chemicals advances the issue of detection and assessment of cancer risk. This expanded characterization includes assessment of genetic toxicity; effects of dose, sex, and species on the absorption, distribution, and excretion of the chemical; and the nature of organ system toxicity. All are essential to the better selection of chemicals for study and the design and interpretation of tests that assess carcinogenic potential.

There is a minimum level of lifetime animal bioassays for carcinogenic potential that must be performed in support of test method development and validation. These, for example, may represent: (1) chemicals selected to test extrapolation parameters from animal studies to epidemiology studies that have a quantitative data base; (2) the retesting of chemicals in newer experimental designs to validate innovative procedures and quantitative data; and (3) the testing of chemicals as part of a verification of data developed from less expensive and more facile cancer bioassays. The initiation of approximately five such assays each year (a total of 20 research tests ongoing at any one time) would appear to be a minimal number to serve this need.

There is also need to continue to develop a data base on chemical carcinogenicity as detected by "standard" animal bioassay. Selection of the chemicals for these bioassays through the NTP chemical nomination and selection process, simultaneously serves the science base, public health, and regulatory need.

The chemical nomination and selection system is a multistage process seeking nominations from academic, industry, labor, and the public sectors, as well as from the regulatory and research agencies participating in the NTP Executive Committee. These nominations are examined at several levels before final selection to assure that the candidates that might yield the most significant scientific information receive the highest priority ranking. Eight chemical selection criteria guide the selection process. All nominations are screened to determine if the chemical has already been tested, is under test, or is scheduled for test either by government or industry. Most chemicals are nominated because information is lacking and potential exists for human exposure. Other criteria include production levels, physical and chemical properties, regulatory and scientific interest, and significance to society.

The initiation of 20 new lifetime tests for public health each year (100 ongoing at any one time) would be a significant decrease from current effort (225 ongoing), yet would represent a reasonable balance anticipating full implementation of the Toxic Substances Control Act. This level of testing also adequately allows for the rapid development of a data base upon which to validate altered bioassay designs or to serve as a standard base for the comparison of the predictability of innovative and quicker approaches to detecting cancer potential of chemicals. The gradual decrease in total number of cancer bioassays should permit broader initiatives in toxicology methods development and validation without significant increases in resources.

In summary, the NTP proposes to place approximately 25 chemicals on test each year. At this level it is believed the NTP can test chemicals which otherwise would not be tested, provide testing necessary to support its methods development programs, and advance the state-of-the-art of chemical toxicology.

TRANS-NIH NUTRITION COORDINATING COMMITTEE

Summary of Plans and Accomplishments

Plans for Fiscal Years 1982 and 1983

The study of hypochloremic metabolic alkalosis will continue and a workshop for scientists, parents, and industry will be held to further define the effort.

The development of scientific copy for public informational fact sheets in the Expanded Foods for Health Project will be implemented.

The office plans to continue to identify areas for further research and bring these to the attention of the scientific community. Future areas to be addressed include nutrition and behavior, and the nutritional support of patients.

Selected Accomplishments

A joint program announcement was developed for a New Investigator Research Award supported by five Institutes--NCI, NIA, NIADDK, NICHD, NIDR--and ADAMHA.*

Seven Clinical Nutrition Research Units are funded for human nutrition research through the new National Program in Clinical Nutrition (three of these were funded in FY 1980).

Automated data retrieval system for all nutrition research supported by the NIH was completed.

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* The following abbreviations are used throughout this chapter: National Cancer Institute (NCI); National Institute on Aging (NIA); National Institute of Arthritis, Diabetes, & Digestive & Kidney Diseases (NIADDK); National Institute of Child Health & Human Development (NICHD); National Institute of Dental Research (NIDR); the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); National Institute of Neurological & Communicative Disorders & Stroke (NINCDS); National Institute of Mental Health (NIMH); Centers for Disease Control (CDC); Food and Drug Administration (FDA); and Veterans Administration (VA).

The office consulted on the development of 27 short video tapes "Eat Well, Be Well," financed by Metropolitan Life Insurance. This represents successful collaboration of Government and industry.

The office initiated and coordinated the presentation of eleven "Scientific Seminars in Nutrition," designed to highlight nutrition research carried out by intramural scientists.

To respond to the Infant Formula Act of 1980 (P.L. 96-359, Sect. 7a), the office provided the impetus for the initiation of a five-year follow-up pilot study at the Clinical Center of infants who developed hypochloremic metabolic alkalosis as a result of being fed chloride deficient formula. This study is being done in collaboration with the NIADDK, NICHD, NINCDS, NIMH, CDC, FDA, and VA.

REVIEW OF PLANS AND ACCOMPLISHMENTS

Accomplishments

FY 79 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training

In order to prepare the FY 1979 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, information on all nutrition research grants, program projects, contracts, centers, reimbursement agreements, research training and manpower development supported by the NIH was computerized. The definition of nutrition research developed by the Nutrition Coordinating Committee (NCC) is used as a basis for data retrieval.

Having completed the data retrieval system, the NCC has now successfully accomplished the three specific functions given in its mandate that have explicit end points: (1) to define nutrition research at the NIH, (2) to develop a policy statement for research and training in nutrition, and (3) to develop a data retrieval system for research and training in nutrition.

Joint Program Announcement for a New Investigator Research Award in Nutrition

A major accomplishment of the NCC is the approval and development of the joint program announcement for a New Investigator Research Award (NIRA) in nutrition. The NIRA is supported by five Institutes--NCI, NIA, NIADDK, NICHD, and NIDR--and ADAMHA. This is the first time that a Joint Program Announcement developed by the NCC includes ADAMHA.

Clinical Nutrition Research Units

A significant development in human nutrition research with human relevance in FY 1980 was the establishment of a new National Program in Clinical Nutrition based on Clinical Nutrition Research Units (CNRU). The concept of the CNRU was developed by the NCC with the participation of NCI, NIA, and NIADDK. Each CNRU consists of the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; educational programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities. Of the four CNRUs funded in FY 1979, three are supported by NIADDK and one by NCI. Of the three additional CNRUs funded in FY 1980, two are supported by NIADDK and one by NCI.

"Eat Well, Be Well" Series

A series of 27 short video tapes, entitled "Eat Well, Be Well," was developed by Amram Nowak Associates under contract with Metropolitan Life Insurance Company in consultation with the NCC. Each of the films presents the scientific state-of-the-art and rationale behind the many aspects of the seven dietary guidelines. The "Eat Well, Be Well" series is an example of successful collaboration of Government and industry.

Scientific Seminars

In order to highlight research in nutrition carried out by Intramural scientists at the NIH and to keep the NCC representatives informed of research developments in nutrition, the NCC inaugurated a new program series called "Scientific Seminars in Nutrition." The seminars are presented during the second hour of the NCC monthly meeting. During FY 1980, the eleven scientific seminars presented on various topics of nutrition represent the diversity of interests of NIH scientists in the Intramural nutrition program. The topics of the seminars included: "The Effects of Obesity on Mortality in the Baltimore Longitudinal Study of Aging," "The Role of the Intestine in Nitrogen Metabolism and Plasma Apolipoprotein Biosynthesis," "The Interrelationships of Vitamin A and E in Maintenance of Retina and Formation of Lipofuscin," "Breast Milk, Infections and Nutrition," "Total Parenteral Nutrition In The Management of the Cancer Patient," "Chemoprevention of Cancer With Retinoids," "Nutrition in the Multiple Risk Factor Intervention Trial (MRFIT)," "Biochemical Toxicology of Ingested Toxins," "Determining The Cariogenic Potential Of Foods," and "Potential Neurotoxicity of Artificial Food Colors."

Subcommittee on Nutrition Education

The Subcommittee on Nutrition Education, in accordance with its charge, reviewed NIH nutrition publications destined for the public.

After a year of deliberation, the Subcommittee on Nutrition Education developed a prospectus on the "Expanded Foods for Health Project," a project that would provide supermarket shoppers and general public with accurate information on nutrition and its relationship to health and/or disease. The NCC concluded that each Institute will furnish to the committee the scientific copy for factsheets with a unifying title and logo. Since this kind of activity is already under way by a number of Institutes, the implementation of the project should be accomplished easily. The review of the materials prepared would be handled by a task force of persons from within the NIH, other Federal agencies, and the scientific community, as well as the entire NCC.

Clinical Center Study on the Follow-up of Hypochloremic Formula Feedings in Infants

At the recommendation of the NCC, the NIH has begun a five-year follow-up study at the Clinical Center of infants who developed hypochloremic metabolic alkalosis as a result of being fed chloride-deficient formulas, namely Neo-Mull-Soy or Cho Free. A pilot study, which will include about 50 infants with documented metabolic alkalosis secondary to feedings of formula deficient in chloride, has begun.

In order to respond to P.L. 96-359, Sec. 7(a) that mandates a study to determine the long-term effect on infants of hypochloremic metabolic alkalosis resulting from infant formulas deficient in chloride, a workshop that will include non-Federal scientists, parents, and industry is planned, in order to:

- Define the population to be studied;
- Determine how best to do the study, i.e., expand the present study or develop a collaborative study with infants to be studied in other centers;
- Develop detailed protocols for the study; and
- Determine how long the children should be followed in order to determine the long-term effect on infants of hypochloremic metabolic alkalosis resulting from infant formulas deficient in chloride.

HHS Nutrition Research Initiative

The purpose of the HHS Nutrition Research Initiative is to develop within the HHS a more comprehensive and effective program of nutrition research and training in order to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other agencies. A committee with members from the six agencies that support nutrition research and training has been given the task to develop a cohesive program for the Department in order to best carry out this initiative in nutrition research.

The NIH is designated as the sponsoring agency to develop the initiative and the NCC Chairman is designated as the coordinator. The agencies designated as cosponsors of the initiative are: the NIH-NCC; ADAMHA; FDA; CDC; the Office of Health Research Statistics and Technology, NCHS-HANES (National Center for Health Statistics-Health and Nutrition Examination Survey); and HRA's (Health Resources Administration) Bureau of Health Professions. The impetus to develop this initiative in nutrition stemmed from the rapidly growing scientific interest, lively public debate on pertinence of nutrition to particular health problems, and evolving Federal efforts to coordinate nutrition research at both policy and program levels.

HHS Nutrition Coordinating Committee

Since FY 1979, the chairman of the NIH-NCC has represented the NIH on the HHS Nutrition Coordinating Committee (HHS-NCC), and the NCC office has provided scientific input to each of the following four HHS-NCC subcommittees: Dietary Guidelines, Nutritional Status Monitoring System, Nutrition Education, and International Health. The NIH-NCC Chairman serves as chairman of the HHS-NCC Subcommittee on Nutrition Research and Research Training.

Plans for Fiscal Years 1982 and 1983

As one of the committees that oversees selected trans-NIH health problems, the Nutrition Coordinating Committee plans to meet monthly in order to stimulate, encourage, and review the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease.

Each year the NCC prepares the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training for the preceding fiscal year. Also, according to its mandate, the NCC sponsors a workshop or conference in an area of nutrition research that is of concern to the Institutes. Such conferences will most likely take place both in FY 1982 and FY 1983.

The NCC will continue to identify areas for further research and bring them to the attention of the scientific community through the development and publication of program announcements, request for applications, and request for proposals. Future joint announcements will address the areas of nutrition and behavior, and the nutritional support of patients.

In order to coordinate research planning and implementation, and thereby strengthen research, a number of health research initiatives have been defined by HHS. The NCC Chairman, as coordinator of the Nutrition Research Initiative, will become increasingly involved in this newly approved activity. Several interagency task forces will be required to begin the implementation of the initiative.

TRANS-NIH RESEARCH TRAINING AND MANPOWER DEVELOPMENT COORDINATING COMMITTEE

Summary of Plans, Accomplishments, and Issue

Plans for Fiscal Years 1982 and 1983

The Coordinating Committee on Manpower (CCM) will emphasize a collective approach to research career development that will assure an adequate supply of future generation scientists. Special attention will be devoted to:

- Increasing the number of physicians electing a research career.
- Improving the clinical awareness of the Ph.D.
- Determining the appropriate balance between predoctoral and postdoctoral research training programs.
- Assessing the role of selected mechanisms to support a training continuum for scientists.

Selected Accomplishments

The Committee met regularly in 12 monthly sessions during FY 1980 with the following results:

- A program of short-term training for students in health professional schools to introduce them at an early stage in their professional development to the advantages inherent in a research career was introduced.
- A summer minority student apprenticeship was implemented through the Division of Research Resources.
- A new lexicon was adopted for the identification of the broad scientific fields in which NIH supports training.
- A review of the K series awards (designed for advanced research manpower development) to consolidate guidelines for all Institutes was initiated.
- It was decided that no overall attempt to raise stipends in FY 1981 would be made.

- In considering an appropriate response to the often posed question of how many NRSA (National Research Service Award) trainees the NIH would support, it was agreed that the National Academy of Sciences projections could serve as a reasonable minimum figure from which to calculate.

Issue

The perceived reduction in the number of physicians seeking training for a research career may threaten the future of clinical investigation. The NIH must develop a plan to encourage M.D.'s to enter research without seriously imbalancing support for other vital research training programs.

Section Four

LEGISLATIVE STATEMENT

The legislative planning function at the NIH consists primarily of:

- Analyzing proposed and enacted legislation for its anticipated impact on NIH activities;
- Developing implementation plans for NIH-relevant provisions of new laws;
- Preparing legislative proposals for extending NIH authorities due to expire; and
- Formulating legislative proposals for effecting necessary or desirable changes in statutes.

Legislative Analysis and Implementation

During the past year, the NIH analyzed a wide variety of pending and enacted legislation for its potential effects on the Institutes.

In the 96th Congress, the bills bearing most directly on NIH operations were Senator Kennedy's Health Sciences Promotion Act (S. 988) and Representative Waxman's Health Research Act (H.R. 7036). These bills would have established authorization levels for each Institute (House), created a President's Council for the Health Sciences (Senate), required the NIH Director to initiate experiments in peer review (Senate), and resulted in a number of other significant changes in NIH operations. Ultimately, however, the bills were distilled in conference to provide a simple two-year extension of authorities for the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI) through FY 1982; reauthorize special NIADDK* activities and create several new programs; and make a variety of technical amendments to non-NIH portions of the Public Health Service Act. The resulting Health Programs Extension Act became Public Law 96-538 in December 1980. Shortly thereafter, the NIH convened its Policy Development and Implementation (PDI) Committee--the mechanism through which NIH develops an operational approach to new laws bearing directly on its activities. Following Departmental approval, the plan formulated by the PDI Committee will serve as a blueprint for effecting specific provisions of P.L. 96-538.

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* National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), formerly called the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD).

Another new law having implications for the NIH and the broad research community is the Patent and Trade Mark Amendment Act of 1980, Public Law 96-517. This law creates a uniform patent policy modeled on the NIH Institutional Patent Agreement (IPA). It also gives nonprofit research institutions, small businesses, and universities the first right of refusal to title of inventions resulting from performance of Government grants and contracts, subject to some limited exceptions. This law signals strong Congressional interest in providing greater research incentives to industry in order to accelerate the diffusion of technology, and could result in increased commercialization of research and attendant benefits for national biomedical research efforts. At present, final regulations for implementing the law have not been issued. It is expected, however, that Public Law 96-517 will raise many issues that the research community will have to address, including whether to delay publication of research results while pursuing patent licensing. Public Law 96-517 and similar legislation bearing on research costs and Government-industry relationships were among science policy issues reviewed by the NIH Director's Advisory Committee during the past year.

There were other NIH-relevant bills introduced in the 96th Congress that proved to be unsuccessful. These included proposals to:

- Require mandatory set-asides of the total research and development budget for use in contracts with small businesses (Small Business Innovation Research Act);
- Limit the amount of research on animals by requiring the use of computer-modeling or other non-animal technologies (Research Modernization Act);
- Create a committee to clear all NIH publications, including submissions to scientific or technical journals (National Publications Act);
- Create a separate Institute at NIH to conduct research on drugs for diseases of low incidence (Orphan Drug Bill);
- Exempt medical records from requests made under the Freedom of Information Act (Medical Records Privacy Bill).

Many issues raised in the 96th Congress remain active, however, and are reemerging in the 97th. The orphan drug bill has been reintroduced, as has proposed legislation to benefit small businesses. These proposals and others reflect continuing Congressional interest in such issues as technology transfer and government-industry research relationships. For example, several pieces of pending legislation are designed to provide research incentives. One of these, the Patent Term Restoration Act of 1981, would extend the life of a patent to include the amount of time it takes the invention to clear the regulatory review process, thereby providing additional inducement to industry to devote resources to research and development. In the same vein, the 97th Congress has already introduced fourteen bills that would use tax credits as research incentives. It is conceivable that legislation will also result from recent hearings on the commercialization of research, with particular emphasis on recombinant DNA technology, sponsored jointly by two subcommittees of the House Science and Technology Committee.

Strong Congressional interest also continues in the NIH role in disease prevention and in the research progress NIH is making with respect to such widespread and costly diseases as cancer, heart disease, arthritis, and diabetes.

Legislative Development for Fiscal Year 1982

During 1981 a major NIH legislative concern has been the reauthorization of the National Research Service Award (NRSA) Program and the Medical Library Assistance Act, which provides the statutory base for the National Library of Medicine (NLM). Currently, four bills that would reauthorize these programs are pending in Congress. The Administration's proposal (S. 1285 and H.R. 3724) would provide NRSA and NLM dollar authorizations through fiscal year 1984 and would make a number of substantive changes in the NRSA program. These include deleting the statutory basis for institutional allowances; making clear that the awards cover not only stipends and allowances, but also tuition and fees; and exempting undergraduate NRSA recipients from payback obligations. At this writing, it is impossible to predict the fate of these reauthorization proposals. None of the bills has been reported out of committee, and there is reason to believe that the programs may be reauthorized as part of the budget reconciliation process. If dollar authorizations are not extended through committee action or the reconciliation process, however, the programs could apparently continue to operate in fiscal year 1982, provided that Senate and House Appropriations Committees effected a continuing resolution for this purpose.

With respect to NRSAs, the NIH is also seeking to amend current statute to permanently define the training awards as scholarships, with attendant tax exclusions, under the Internal Revenue Code. The IRS has not viewed NRSA awards as scholarships, since obligatory payback requirements were introduced into the program. Through a series of temporary exemptions, however, NRSAs have yet to be subject to full taxation. Through the legislative development process, the NIH is seeking a permanent NRSA tax exemption in order to maintain the current net income level for pre- and post-doctoral NRSA recipients and continue to attract the most capable and promising students to biomedical research careers. The proposal for this legislative change, which the NIH has long sought to achieve, has been approved by the Department and is awaiting action by the OMB.

Legislative Development for Fiscal Year 1983

The formal NIH legislative planning agenda for this year has also included development of legislative proposals to take effect in fiscal year 1983. The NIH has submitted to the Department proposals to extend for three years the NCI and NHLBI authorities due to lapse September 30, 1982. Other legislative recommendations concerning NCI included proposals to increase the time limit on NCI center grants from three to five years and to increase administrative flexibility by permitting the NCI Director to approve grants totaling no more than $50,000 in direct costs.

Legislative Statement

The fiscal year 1983 legislative planning package for NIH also includes proposals to:

- Amend the Freedom of Information Act to prevent the premature release of preliminary scientific and clinical trial data;
- Ensure that all NIADDK program areas are mentioned in statute;
- Change statutory language to be consistent with the fact that the NIADDK Council reviews and approves grant applications and not contracts;
- Change the due dates for NIADDK annual reports to as soon as practicable rather than 60 days after the end of the fiscal year;
- Change statutory requirements so that annual reports currently required of NIADDK are prepared biennially;
- Amend the PHS Act to authorize the Secretary to award grants for the purpose of carrying out scientific peer review;
- Permit employees of the Division of Computer Research and Technology who are responsible for 24-hour maintenance of NIH computer capabilities to monitor computer programs from their homes;
- Extend the Federal Physicians Comparability Act of 1978;
- Permit advance of funds to the NIH Services and Supply Fund.

Proposals favorably reviewed by the Department will be sent to the OMB for final consideration. Following OMB approval, they will be transmitted to Congress for introduction on behalf of the Administration.

PROCEEDINGS OF THE
ADVISORY COMMITTEE TO THE DIRECTOR, NIH
on
COSTS OF BIOMEDICAL RESEARCH
and
GOVERNMENT-INDUSTRY RESEARCH RELATIONSHIPS

Preface

The following pages contain the proceedings of three meetings of the Advisory Committee to the Director, NIH, held on March 16-17, June 8-9, and October 1-2, 1981. The Committee's activities are closely linked to the NIH and HHS health research planning efforts. It consists of 16 members drawn from diverse fields pertinent to the NIH mission, including biomedical and behavioral research, medical practice, the social and physical sciences, medical and other higher education, and biomedical communications. Among the members are persons knowledgeable about such matters as applicable law, standards of professional conduct and practice, and public health. The Committee is chaired by the Director of NIH.

As a public forum held approximately three times a year to advise the Director, NIH--and through him the Secretary, HHS, and the Assistant Secretary for Health--the Committee functions in a manner analogous to the Advisory Councils of the individual Institutes, except that it does not recommend approval for research grant applications. Instead, its advice centers on policy matters pertinent to NIH mission responsibilities and is intended to reflect a diversity of informed viewpoints on a wide range of issues. In addition, the Committee provides a framework for review, evaluation, and policy development on general or specific aspects of NIH activities.

During the past five years, the Committee has dealt with such key issues of health research policy as the initial preparation and revision of NIH guidelines for recombinant DNA research, development of a strategy and set of principles for HHS support of health research, and consideration of measures to provide a more stable foundation of support for research at the Nation's academic institutions. Pertinent proceedings from these earlier meetings were published in special planning documents.

The 1980 proceedings of the Committee, devoted largely to an examination of Government-university relationships, were published as a supplement to the NIH Research Plan for FY 1982-84. Those proceedings reflect the work of the Committee in examining cooperative research relationships with industry and Government-university relationships. As the minutes indicate, two working groups were created by the Director, NIH, in March 1981, under the aegis of the Committee: (1) a Working Group on Cooperative Research Relationships With Industry, and (2) a Working Group on Costs of Biomedical Research. Interim reports of both working groups were considered by the Advisory Committee on October 1 and 2, 1981.

Based on recommendations of the Advisory Committee, NIH will explore an array of potential changes in the system of research support. Among the major foci of interest will be reimbursement of indirect costs, vesting of additional authorities and responsibilities in awardee institutions, and a trial of the Fixed-Obligation Grant concept. While some of these initiatives could be taken under present NIH and PHS authority, others would require OMB, GAO, or Congressional approval.

Taking into account the Committee's recommendations, NIH is also considering the development of special patent policy guidance to grantees as an aid to implementing the new patent law and strengthening research relationships. The Committee will continue its exploration of the relationships among government, universities, and industry.

These proceedings and the two reports of the working groups (issued separately) constitute an integral part of the NIH planning process for program strategies. The Committee will continue its vital role in this regard.

MINUTES OF THE
42d MEETING OF THE ADVISORY COMMITTEE
TO THE DIRECTOR, NIH

March 16 and 17, 1981
National Institutes of Health

GOVERNMENT, UNIVERSITIES, AND INDUSTRY:
National Institutes of Health
Cooperative Research Relationships

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Forty-Second Meeting of the
Advisory Committee to the Director, NIH
March 16-17, 1981

SUMMARY OF ISSUES

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I. PATENT POLICIES

A. All issues in this section should be considered in the framework of the Patent and Trademark Act Amendments. These change existing practice in important ways.

B. Allocation of Patent Rights

- IPAs are now statutorily mandated for small business and nonprofit organizations.

- A major issue raised by Mr. Hutt and Mr. Whale was that the statute did not extend IPAs to large business organizations. Mr. Hutt urged the concept of a Business Patent Agreement (BPA), and during the NCI presentation he noted that NCI in effect has such an arrangement with its contractors in the orphan drug program. Thus, the Department could approve this policy without a statutory mandate.

- Coupling of Funds. Dr. Fredrickson raised the issue of the allocation of patent rights when industry and Government share support for a project at a Federal laboratory, at a university, and in industry.

  What processes now govern these situations, if any, and what changes will occur under the Patent Act Amendments?

- Federal Laboratories. Dr. Fredrickson asked the impact of the new amendments on inventions developed in Federal laboratories. Apparently, there will be no change in policy here and Federal Management Procurement Regulations will apply as they have since the 1950s. Is there a need for review?

- Federal Patents. Mr. Whale raised the issue of the large number of Federal patents (8,000) and whether it was necessary for the Federal Government to apply for so many when, in fact, some were not used. Is there need for review of policy here?

- HHS General Counsel Review of IPAs. Mr. Staats and Mr. Hutt noted that in 1977 HHS began a review of IPAs with an apparent intent to limit their further application. The new amendments now mandate those policies. But what is the status of the HHS review? And how will the new amendments be interpreted in light of that review?

C. Patent Royalties

- Allocation Among Scientists and University. Dr. Temin raised the question of what should be the fair rate of return for the scientists at the university. Current HHS IPA agreements specify a range, but the new amendments, when implemented, may eliminate Federal guidance. However, Mr. Grinstead noted that the Department has been petitioned by some industries to "march-in" and take away the patent rights from a university because of their "outrageous" royalty demands on inventions developed with Federal support. What does the statute provide and what will the new Federal regulations state in this instance? Drs. Cheston and Andrews and Mr. Bremer all strongly defended the royalty return for the university as essential to support patent programs of the universities and nonprofit organizations and to assist the universities to support the research environment that becomes even more costly without complete recoupment through the indirect costs charged to research.

- Allocation of Royalties Among Universities and Industry. Here the issue is both allocation of patent rights and the royalty rate structure. Dr. Andrews pointed out that there are disagreements here, for some corporations demand full patent rights with waiver of royalty for any inventions developed under industry-sponsored programs. The universities' view is that they provide the education and environment and in return should have the right to any inventions and receive a fair rate of royalties. What rules govern? Do universities have standard rules?

- An important issue is whether the Government can recoup some of its investment in research. This question was raised, particularly by Dr. Temin, after the NCI presentation, in which it was pointed out that NCI had invested in the development of a drug and assigned the rights to a corporation. Does this need to be further explored? Dr. DeVita indicated that this question was not considered during the '70s, when the return was not great. In the '80s, with more effective drugs and a better return, perhaps it needs to be considered. Dr. Fredrickson noted that the new amendments make it less likely for recoupment to occur administratively, since provisions for recoupment were all struck before they were passed.

D. Licensing

- General. There was a good deal of discussion about the need for a longer period for patent protection and licensing. Many of the representatives from industry noted the increasing time requirements for Federal regulatory approval (FDA requirements, for example) and indicated a need for help. It was noted that bills are pending and have been introduced in the past to permit longer periods. It will be important to follow legislative developments here and to determine the likelihood of passage. Mr. Bremer pointed out the need to consider extension of the period of an exclusive license for the equivalent of time that an issue is before a regulatory agency. As an example, while a New Drug Application was pending before the FDA, the running of the exclusive license granted would be tolled until the regulatory proceeding had been concluded.

- Compulsory Licensing. A number of questions were raised here, especially in light of the Federal Government's "march-in" rights. Judge Markey pointed out that a system exists in Holland whereby patent rights are not activated until there is a possibility for licensing. Dr. Andrews, Mr. Bremer, and others noted the "late bloomer" phenomenon: a patent is issued for an invention that isn't ready for its licensing because of the state of the art, but where successful applications ultimately occur. Dr. Bremer also noted how difficult it is to license an invention. Mr. Grinstead cited an example of possible use of the "march-in" option by the Federal Government where a licensee has not acted in a timely fashion to move the product, while a foreign competitor has. What should be the policy here?

E. March-In Rights

- These provisions under the IPAs and the new amendments were a source of considerable discussion. In Dr. Siekevitz's view, these should be carefully examined as a means of providing Federal oversight. Mr. Hutt, on the other hand, was most concerned lest this provision cast a cloud on inventions developed under Federal support. Mr. Grinstead cited examples regarding the use of this provision for licensing and royalties. Mr. Cheston supported the concept, noting that it was important for industry to recognize that march-in may occur if the license isn't properly handled. There was some dispute about how often this provision has been invoked. Evidently, it has in fact rarely been applied. Dr. Andrews noted that in his experience Purdue has used it several times to protect the public interest, and he believes it is a worthwhile provision. What should be the guidelines here? What does the new statute say? What regulations will ultimately apply? And how will HHS implement these?

F. University Patent Administration

- Dr. Fredrickson asked Mr. Bremer whether there are units at major universities analogous to the Wisconsin Alumni Research Foundation. Mr. Bremer responded that there are a variety of administrative units or functions at universities ranging from his own model to a single patent administrator. A need exists here for an analysis of patent administration structure within the universities, the Government, and industry.

G. International Aspects

- Dr. Fredrickson asked Judge Markey and others about allocation of patent rights in foreign countries and the resolution of patent disputes among countries. There seems to be little information on the nature of patent systems. And there is no forum for adjudicating patent rights internationally. Can we get additional information here? Do such things as IPAs exist in Western Europe, for example?

H. Protection of Proprietary Information

- General

  There was a good deal of general discussion about the open system of communications in the biological sciences that now exists in this country and the impact of patenting on that system. Dr. Shaw felt that the patent system does indeed promote disclosure. Others like Dr. Siekevitz were most concerned about the chilling effect on early communication of research results. Dr. Andrews noted this was a problem for the university, and especially for junior faculty who must publish as quickly and often as possible in order to be promoted and get tenure. Dr. Bennett also pointed out that this was a key question in regard to industrial support. Dr. Smith cited the problem encountered in the Exxon agreement with MIT relating to the protection of proprietary information where graduate students are doing the work. Guidelines were developed to protect the information and to meet the needs of the graduate students, but it is a tough area. Dr. Lowe said this is the key area for NIH concern. What will be the impact on the review system? Much analysis needs to be done as NIH considers its policies here. Of all the issues raised by the participants, it is probably the most important.

II. GOVERNMENT/UNIVERSITY/INDUSTRY SUPPORT FOR BIOMEDICAL RESEARCH: FINANCIAL AND ADMINISTRATIVE MECHANISMS

A. Introduction

- There was general agreement that it was the appropriate role of the Federal Government to support fundamental research at universities and for industry to do the applied research and technology transfer. It was agreed that industrial support could in no way substitute for the heavy Federal investment in fundamental research at universities. Drs. Wilson and Bennett in particular emphasized this point.

B. Nature of Biomedical Research

- Dr. McDermott and others pointed out the differences between biomedical research and physics or chemistry. Dr. McDermott noted that there were a number of disciplinary barriers among the various subdisciplines and subspecialties in medicine. Further, biomedical research involves patients, which is an important consideration; also the biomedical scientists have traditionally looked to the Federal Government for support, whereas the physical and chemical scientists have been dealing with industry for years. Dr. McDermott observed, too, that once the research pays off in terms of a cure, scientists then move on to attack another problem and do not concern themselves with making the treatment more cost-effective. How should these problems be addressed by the NIH and the universities? How can the biomedical scientists learn more from the physical and chemical scientists on the problems and successes they have had in working with industry?

- Another major issue related to establishing priorities in biomedical research. Dr. Sokol urged greater industry participation in decision-making by NIH and universities on health research programs and priorities. In his view, there should be more attention to applied research. Dr. Vagelos urged the development of some mechanism for setting priorities--for example, in the area of vaccine development. How should the NIH approach this matter? Dr. Krause noted that the Institute of Medicine (IOM) will be convening meetings to assist in the area of research priorities for vaccines that would involve Government, universities, and industry. Is this a possible model for consideration? Dr. Orbach urged as a matter of high priority greater university attention to research directed at assisting regulatory decision-making in the health area. Mr. Throdahl concurred with the suggestions. Universities must try to develop a science base to assist the regulators, and there needs to be some form of collaboration in setting research directions here. What, if anything, should the NIH be doing in this area? Is this something for the NTP to consider and promote more broadly?

C. Scientific Collaboration

- As noted above, the Committee devoted attention to the relationship of biomedical scientists to industry. Dr. Andrews observed that before World War II much of university-based research was supported by industry, and many scientists had extensive contacts with industry. After the war, a new generation of scientists emerged concerned with fundamental research sponsored by the Federal Government. Thus, this generation lacks knowledge of and has few contacts with industry. Dr. Temin suggested that perhaps NIH should consider initiating meetings or other measures for increasing interaction between university and industrial scientists. (What other possible mechanisms can be addressed here?) There was strong agreement that for collaboration to succeed it must be at the scientist-to-scientist level with guidance and support from the administrators. Dr. Bennett, agreeing with Dr. Andrews, noted the great difficulty in getting these scientists together to collaborate. Dr. Sanderson also recognized this state of affairs and said that the NSF, through a variety of administrative mechanisms described below, has attempted to enhance scientific interchange and collaboration.

D. Possible Federal Roles To Enhance Collaboration

- Dr. Sanderson cited several NSF programs designed to stimulate collaboration: (1) grants to universities to stimulate industry-university participation in joint research ventures at the individual project level, (2) centers of scientific excellence that eventually would become self-supporting through industry, (3) targeted research in certain areas, such as the automotive industry, and (4) generic technology centers. Are any of these models relevant to the NIH situation? There was little enthusiasm among several DAC participants for the Stevenson/Wydler proposals for technology innovation centers.

- The NIAID presentation on the hepatitis B vaccine raised the issue of whether this might be a prototype for NIH collaboration in the future. Many felt it was an idea that could not be achieved in other research areas, though perhaps elements of it could be considered. Dr. McDermott strongly recommended that there be a role for NIH, perhaps along the model of the NIH consensus development exercises. NIH might assume the role of bringing together top-flight people from Government, industry, and universities to address tough research problems of pathogenesis. The thrust would be to examine what we know, where the weak links are, and where there may be some opportunity for various parties to pursue research leads consistent with their interests and investments. How should NIH react to this suggestion? Should OMAR play this role in relation to the technology consensus exercises? Dr. McDermott believes the payoff here would be great because it would not require a lot of Federal money and would be something in which all parties could join and from which all would benefit.

- The NCI presentation on the orphan drug program raised a number of questions. Should this model be explored in relation to other research areas? Dr. Fredrickson said NIH current funding would not permit an orphan drug approach across the board without some additional funding or commitment from industry. Dr. Vagelos pointed to orphan vaccines as an area where Federal support would be indicated. How should this issue be pursued? Mr. Staats indicated GAO is doing a study of the NCI program as a possible Federal model for other agencies; that study is due in the fall. Clearly, we need to monitor it closely.

- Further, Mr. Staats indicated that the GAO has under review Federal programs for technology centers, and is examining the best Federal investment here. This study is due in the fall and should also be carefully reviewed.

E. University/Industry Models for Collaboration

- Possible models considered were the Exxon-MIT and Monsanto-Harvard agreements. Should these be more fully explored for clues to Federal-industry interaction? Does the greater biomedical research community need to know more about these agreements?

- There was a good deal of discussion about the recent application of venture capital to university-based research on recombinant DNA. Dr. Siekevitz wanted to know what the NIH policies were here. Dr. Fredrickson said that currently there is no comprehensive policy and that the purpose of this meeting is to consider policy alternatives. There may need to be several complementary policies. A number of participants expressed concern about venture capital investments. Dr. Andrews felt that such investments may tend to distort university/industry relationships. Dr. Smith noted that indeed MIT had tried in the past to create MIT research corporations and had found the result not a very happy one. There were problems of conflict of interest with the university and the owner of the firm. The university had to consider its responsibility to itself as an educational institution. Dr. McDermott suggested that perhaps universities need a code of ethics to govern these situations. Dr. Smith further noted the phenomenon that not all industrial investment at MIT is for the promotion of applied research; however, the psychological effect on faculties is sometimes that they need to do applied research. Dr. Temin noted that some faculty want to work part-time so that they can also work part-time in industry. Such division of time will have implications with respect to the percent effort of the principal investigator on existing and potential NIH grants. University and industry views are in conflict regarding patenting. A real scientific-legal thicket is developing here. How should NIH approach this subject? Should the universities consider guidelines for themselves, as Dr. McDermott suggests? What should be the NIH role?

- There was strong support among participants for tax bills introduced in the last session of Congress and reintroduced this session that would allow credits to industry if they provide support to universities for basic research. Another bill, introduced by Representative Shannon (Mass.), would give tax credits and depreciation for instruments donated to universities, and would also allow credits for funds provided to universities for instrumentation. Dr. Bennett noted that Canada provides a $1.50 tax credit for each $1 industry invests in university research. Dr. Sanderson noted that if the Vanik bill had passed, estimates are that the annual industrial investment in university research would have doubled. We will need to monitor these Congressional activities closely and consider the impact of this on NIH-funded research at universities.

F. International Aspects

- Dr. Fredrickson inquired about arrangements in the European countries for involving government, university, and industry in collaborative research relationships. There is not much information on this subject. Dr. Smith noted that there is often very close collaboration between industry and academia, particularly in West Germany, where leading industrial scientists frequently hold academic chairs at the university. How should NIH pursue the international aspect? Can something be learned from the Europeans or the Japanese?

ADVISORY COMMITTEE TO THE DIRECTOR
Minutes of the 42nd Meeting, March 16-17, 1981

Prepared by
Joseph G. Perpich, M.D., J.D.
Executive Secretary

The 42nd meeting of the Advisory Committee to the Director, NIH (DAC), was held at the National Institutes of Health, Bethesda, Maryland. Dr. Donald S. Fredrickson chaired. (See Attachment A for list of members and consultants and letter of invitation.)

First Day: Morning Session

Introduction

Dr. Fredrickson opened the meeting by commenting that over the past five months he has had responsibility for briefing the transition teams and the new HHS Secretary and Assistant Secretary for Health on the role and mission of NIH, particularly in terms of its budget. Through these exercises a good deal of attention has been paid to the complementary relationships of NIH, the academic community, and industry in the support of health research. This meeting derives not only from the Committee's continued examination of government and university relationships as they extend to industry, but also from the briefings of the transition team and the Secretary on the role of industry in support of health research, particularly in light of limitations on Federal spending generally and the implications for health R&D.

Dr. Fredrickson presented four charts that summarize the national cost of health R&D in different perspectives. (See Attachment B.) Of the $7.9 billion spent for health R&D in 1980, approximately $4.7 billion came from the Federal Government and $2.4 billion from industry. NIH contributed approximately 40 percent of the $7.9 billion; other Federal agencies, 20 percent; and industry, 30 percent. As performers of R&D, universities accounted for approximately 38 percent, industry 29 percent, and Federal laboratories 16 percent. Of the university research, totaling $3 billion, the Federal Government contributed approximately 79 percent and industry 3 percent. Of the $2.25 billion spent by industry, 84 percent came from industry sources and 16 percent from Federal. Examination of health R&D funds used by universities in 1960, 1969, and 1980 shows that the Federal contribution to their research rose from 61 to 79 percent. Over the same period, the share of industry expenditures coming from the Government rose from 11 to 17 percent (1969) and has since dropped to 16 percent.

Dr. Fredrickson remarked that the data provide an excellent framework for the Committee's examination of relationships among the Federal, industrial, and academic sectors. Presentations by representatives of these sectors during the meeting, with intermittent comment and discussion, should provide an excellent perspective not only of government and industrial support, but of policies related to profit versus nonprofit approaches; to support of fundamental science versus applied and developmental science; and to the respective roles of government, industry, and universities, with attention to present relationships and how they may change. Dr. Fredrickson concluded that the attendees would learn a good deal about the basic issues concerning support and the nature of support among the three parties.

Perspectives on the Patenting of Biological Inventions

Howard T. Markey, Chief Judge
U.S. Court of Customs and Patent Appeals

Dr. Fredrickson introduced Chief Judge Howard T. Markey, noting the importance of his perspectives in light of the Supreme Court decision that opened the possibility of patenting biological inventions. (See Attachment C for the decision by the Supreme Court in Diamond, Commissioner of Patents and Trademarks, v. Chakrabarty.) Chief Judge Markey opened with an overview on the importance of technology and the patent system for the economy of the United States and international trade. He pointed out that in 1968 the United States led the world in international trade, with 23.9 percent of the exports. By 1978 the United States had fallen to sixth place, with 14 percent. Judge Markey added that during this period fewer than half the applications for U.S. patents came from U.S. inventors, a reversal of the previous pattern. He commented that this decline had prompted public and private concern about the Nation's technological base and had spurred attempts to promote innovation and new technology and, through inventions, investment risk and profit.

Judge Markey emphasized that the American patent system exists to encourage disclosure of information, although too often people believe its thrust is to prevent disclosure. He urged that the Committee and the representatives from the universities pay more attention to using the patent system for university-based inventions. Heretofore some have been unwilling to become involved in patent matters, with concern about issues of disclosure or monopoly. He noted that patents do not provide for wrongful monopolies. The patent system grants an inventor the right to exclude others from using the invention for a period of 17 years, which tends to stimulate invention while making knowledge available to all. There has been too much confusion about the bases for the patent system. In universities, there is concern about a perceived conflict between the role of imparting knowledge and that of making a profit--a conflict of educational with industrial goals, where there is a need for profits. But he pointed out that universities run press operations, which seem to have created no problem, and he added that both Jefferson and Lincoln were inventors and held patents.

Turning to the issue of recombinant DNA research, Judge Markey noted the public concern about potential risks from this technology and alluded to the Cambridge City Council's overview and rules concerning the research. In the Judge's view, science provides knowledge, and knowledge per se cannot harm. It is the application of knowledge that may have deleterious consequences. There is need to scrutinize and oversee the application, but not the fundamental scientific search for knowledge. He pointed out that one should be aware that German courts in 1975 approved the patenting of manmade living organisms and that Japan in 1979 permitted by statute the patenting of organisms and products. Thus the United States Supreme Court decision in Chakrabarty was not the first action to permit such patenting in the world. However, it reflects developments throughout the world to extend patent protection in this area.

Judge Markey commented that the Chakrabarty decision by the Supreme Court is very narrow in that it does not speak to whether an organism is patentable, but only admits the application to the Patent Office for consideration. It still has to meet the tests for granting a patent: novelty, usefulness, and unobviousness. Thus the Supreme Court opened the door to the Patent Office, but the hurdle of obtaining a patent remains.

Judge Markey noted that basic patent law provides for patenting any process, manufacture, composition of matter, or other substance created by man, or improvement thereon. In the Chakrabarty case the insertion of four plasmids in a Pseudomonas bacterium gave it the ability to degrade oil, which it could not have done otherwise. As Judge Markey pointed out, the process did not strictly employ recombinant DNA, but it did involve genetic engineering. The issue arose whether this organism as living material could be considered for patenting. The Patent Office had said that under the law it could not. The Court of Customs and Patent Appeals and the Supreme Court, however, ruled that it could--that its "aliveness" did not prevent consideration of a patent. The Judge noted that the Patent Office is now developing guidelines on the basis of the Supreme Court decision. Essentially, it will now hold that an application cannot be refused on the sole ground that the invention is "live."

Judge Markey added, however, that the Committee should recognize that not everything is patentable; abstract ideas, physical phenomena, or mathematics are not. He emphasized that only a product or process created by man may be considered for patentability and that it must meet the previously mentioned tests of novelty, usefulness, and unobviousness. Judge Markey concluded that the U.S. patent system is the finest in the world and ought to be used by universities as well as industry.

Committee Discussion

Dr. Temin asked who should receive the profits from an invention developed at a university: the professor or the university. Judge Markey replied that this was a policy question. He said both clearly have an interest in the success of the invention and both could share in the proceeds. As a private attorney, he had urged corporations to share with the inventors--their employees--as an incentive beyond salary. He would probably have advised the same for universities.

Mrs. Wexler noted that university presses traditionally have provided all the profits to the author rather than the university. Dr. Andrews noted that while that may be true historically, the university rather than the author currently receives the profits in such areas as film and study guides.

Dr. Siekevitz asked the Judge to explain further the patentability of a process or product--for example, whether the process of the implantation of an ovum in the uterus is patentable. Judge Markey stated that he cannot give his views on hypothetical cases because frequently such a case will come before him and he cannot prejudge an issue. He did note that in the Chakrabarty case the Patent Office had granted patent claims by Chakrabarty for the method of inserting the plasmids in the bacteria and also for the combination of the bacteria with some other matter. However, the office declined to patent the microorganism itself on the basis of "aliveness." Thus, it was the process that the Patent Office approved. This is the case in other countries as well--e.g., Germany and Japan. He also noted parenthetically that about 30 years ago the Patent Office had indeed granted a patent for a living yeast organism that was not taken into account in the Patent Office's decision in this case.

Referring to Judge Markey's comment that the U.S. patent system was the best in the world, Dr. Sokol asked whether in the Judge's view any improvements were needed. The Judge reaffirmed his high opinion of the U.S. patent system, but said that, of course, changes could be considered. He could not take a particular view on a number of possible statutory changes--e.g., there is now under consideration a statute that would extend the period of patent protection from the current 17 years from the date of issuance to 25 years from the date of filing. He noted that the Constitution gives the patent to the inventor rather than the assignee, whereas most nations grant it directly to the latter. These are important issues that will continue to be debated. There are also issues involving other countries. At one time in Great Britain, one might obtain a patent of introduction on an American invention, even though he had done none of the work.

Dr. Sokol remarked that there are issues involving preexamination and compulsory licensing and asked whether the Judge had any comments. Judge Markey expressed reservations about whether compulsory licensing is possible, but said that preexamination may be forthcoming. In Holland, for example, one files for a patent, but no action is taken until there is exploitation. Once the exploitation begins, the invention is reviewed for patentability. There may be some merit to this approach, especially in view of the granting of 75,000 patents a year in the United States, with few actually being exploited. Perhaps we should consider the Dutch experience.

Dr. Fredrickson asked Judge Markey how competing patent claims in various countries are adjudicated. Is there some way to handle international disputes involving patents? Judge Markey responded that there is no system for reaching a final determination that would hold worldwide. There are opportunities for arbitration through such bodies as the World Intellectual Property Organization. Basically, each patent is effective only in the issuing country, and there is no higher body to issue a patent internationally. At the Hague Court of Justice, there are decisions on a country-to-country basis, but not individually. Through the European Economic Community (EEC), however, a patent system for Europe is growing that would provide for a patent in all member countries.

Dr. Vagelos noted the question of exclusivity as it applies to the drug industry. He added that the period from issuance of a patent to marketing of the drug has increased to about 8 to 10 years. Thus, there is an increase in the time and money required to market a new drug. He asked whether Judge Markey had any views on patent restoration acts that would provide for more lead time. The Judge commented that this is an important question for Congress, especially in the drug area. He understands that rules regarding new drug applications and drug review for the regulatory process impede the marketing of inventions--sometimes for as long as eight years. There are bills in the Congress that would add patent years lost in complying with Government regulations. Under the Secrecy Act, orders are issued that do not permit the exploitation of an invention involving national security. When such orders are lifted, if indeed they are, then the inventor must go to the Congress on a case-by-case basis to have the patent extended for the time lost under the order, and the Congress generally approves such requests. The Restoration Act would provide a statutory basis for granting such extensions generically. There is a precedent here, and there seems to be greater support in the Congress for such action.

Dr. Siekevitz asked about the legality of NIH's use of march-in rights. Judge Markey responded that the patent confers title, either to an individual or an organization. If the title is vested in NIH and NIH assigns the patent or title to a university, it can do so subject to conditions it wishes to set. March-in rights may be one of those conditions for patents granted to university scientists who develop an invention with Federal support. Dr. Siekevitz continued by asking whether the law should be changed so that if a patent is not exploited within 5 to 8 years, the rights can be taken back. He thought there should perhaps be a limit on the use of the patent--in effect, compulsory licensing or loss of the patent rights. Judge Markey replied that, indeed, one could change the law, but it is not clear whether compulsory licensing would be feasible or desirable. An invention may not have immediate use, he pointed out. There are cases where it can be used commercially only when the state of the art has caught up with it.

Dr. Fredrickson asked the Judge whether a living organism that one discovers is patentable. The Judge responded that it is not. He cited a case in which the inventor used two bacteria in a preservation process. The court ruled that the bacteria were merely doing what they had always done, and therefore the process was a product not of man but of nature. The process or organization must be manmade. Dr. Fredrickson then asked for his views on a means of accelerating the exchange of genetic material among bacteria, creating genetically different organisms. Judge Markey said the key here is that man had intervened to produce these changes, and therefore, the application for a patent would have to be considered. Then it would have to meet the three tests of novelty, usefulness, and unobviousness.

I. CONGRESSIONAL AND ADMINISTRATION INITIATIVES IN PATENT AND TECHNOLOGY POLICIES

Perspectives from the General Accounting Office

Elmer B. Staats
Comptroller General of the United States (retired)

Mr. Staats, who retired from the GAO in March after 16 years as Comptroller General, opened by noting the post-World War II phenomenon of enormous Federal investment in R&D through NIH, NASA, Defense, and the Atomic Energy Commission. In 1961 President Kennedy's science advisor recommended the establishment of a task force to develop administration policies on patents. Such a task force was created, and its recommendations led to the 1963 Presidential Memorandum and Statement of Government Patent Policy. This was revised in 1971. These documents provided administration policy because there was no statutory policy for the Executive Branch. The 1963 memorandum stated that there should be a consistent patent policy for all R&D except for areas covered by specific statutory mandates, such as the atomic energy field. Mr. Staats noted that a number of policy options were considered, ranging from the Government's dedicating a patent to the public to its assigning the rights to the inventor.

The memorandum suggested creation of a patent advisory panel for the Federal Council of Science and Technology. Such a committee was created in December 1965, mainly comprising representatives of the research and development agencies. It examined three policy questions relating to patents--namely, industry interests in Government patents, the effect of patent policy on industrial participation in Government-sponsored research, and the effect of patents on competition. A contract was let to Harbridge House. The report of the study in May 1968 disclosed that allocation of patent rights varied among Federal agencies. The Committee recommended that the Government allocate and provide for patent rights and licensing to the inventor in order to facilitate transfer to the marketplace. In August 1971 President Nixon approved these recommendations. Until this time, Mr. Staats said, there was no consistent Federal policy regarding patents.

In 1971, Mr. Staats continued, the Commission on Government Procurement, created statutorily by the Congress, reviewed the issue of a possible legislative approach. It became clear that the question of ownership of an invention developed under Government support was a very sensitive one. It was largely a philosophical question of whether the Government should obtain the patent rights because of its support or whether it should assign them and thereby facilitate transfer to the marketplace. After hearing all sides the Commission unanimously recommended that the title be assigned to the inventor or contractor, with march-in rights for the Government under specified circumstances. However, no legislation was passed.

In 1979 GAO was asked to conduct another review of possible patent legislation. This was prompted by concern about U.S. dollar payments and improvement of national productivity. On the basis of that study, Mr. Staats presented GAO recommendations before the Committee on the Judiciary considering S.414--the University and Small Business Patent Procedures Act. (See Attachment D for Mr. Staats' statement on S.414 and his November 28, 1979, public lecture on current national issues involving science and technology.)

The GAO had found that patent policy was not uniformly implemented and that the allocation of rights varied from agency to agency. Further, by 1968 hundreds of compounds had been developed but not tested by the drug companies because of their lack of exclusive marketing rights. In view of these facts, DHEW, with support of the Secretary and the President, offered institutional patent agreements (IPAs) to permit universities to retain title. As of October 1978, 72 universities held IPAs. The National Science Foundation had instituted the same agreements in 1973. IPAs seem to be highly useful, and the Federal procurement regulations in 1978 generally adopted policies to promote them. Mr. Staats noted, however, that in July 1978 the Department of HEW began reconsidering IPAs and that backlogs of cases began to accumulate as the Department reviewed the matter more carefully. In response to GAO inquiries, the Department stated that the purpose of the review was to make sure competition was not stifled in those cases where it could bring the fruits of research to the public faster and more economically.

Mr. Staats remarked that as a result of this review decisions on allocation of patent rights are taking 8 to 15 months to complete. He added that the Pharmaceutical Manufacturers Association has told the Department that exclusive interests are essential to the drug industry in order to license and market new drugs and that the HHS patent policy should not therefore restrain invention. It urged that the IPA policies be reaffirmed. Mr. Staats also stated that 8,000 inventions have been disclosed to the Government, but only a handful have been licensed. It is essential that patent policy reflect the need to allocate these patent rights so that licenses can be taken up by the private sector and the drugs marketed. The GAO study concluded that a uniform Federal patent policy is long overdue and that the Congress should act to provide a statutory framework.

Mr. Staats said that with the passage of S.414 the Federal patent policy has been clarified. He did note that the GAO, in commenting on S.414, said that some other provisions would have been most useful--namely, a comprehensive policy for all Federal R&D, not only for small business and nonprofit organizations but for all Government grantees and contractors. Further, there should be a recapture provision.

Mr. Staats remarked that the bill provides for the Comptroller General to be informed and to audit decisions when the Government agency decides to retain title. For purposes of use of these patents, the Federal Government has a paid-up nonexclusive license for Government use anywhere in the world, and this provision reserves use of the invention at no cost to the funding Government agency. Mr. Staats briefly summarized the provisions for march-in and for giving preference to U.S. industry. In sum, he said, this bill is a major change that establishes a national policy--limited, however, to small businesses and nonprofit institutions. The concerns that led the Congress to pass this bill, he said, also led it to pass the Stevenson-Wydler bill providing Federal assistance for developing cooperation among industry, government, and universities and creating centers for technology innovation. GAO supported this legislation.

Mr. Staats described two ongoing GAO studies. The first is a review of Federal drug development programs, particularly the orphan drug development program of the National Cancer Institute. Questions the GAO is addressing in this study are the following:

- Is the NCI program a model for other Federal drug development programs?
- What impact do Federal efforts here have on drug firm participation?
- What is the Federal role in the development of orphan drugs?
- What is the pharmaceutical industry's role in their development?
- Is the Federal Government compensated sufficiently for its efforts in developing these drugs?

The report is scheduled for delivery to the Congress in August.

The second GAO review related to possible Federal efforts to stimulate university and industrial interaction. There is going to be a two-stage review and study examining three types of university-industry collaborative effort: cooperative R&D programs, university extension services, and research parks. The report is due in the late fall.

Finally, Mr. Staats reported that a number of bills have been introduced in the new Congress which continue efforts in this area from the last Congress. Senator DeConcini has introduced a bill for a unified court of patent appeals; Representative Kastenmeier, a patent restoration act. Congressman Rosenthal introduced a bill on licensing requirements for the pharmaceutical industry, and Senator Danforth on creation of an independent Patent Office. Hearings are being held on all of these.

Committee Discussion

Dr. Temin referred to Mr. Staats' statement that of 8,000 Government patents, only a handful have been licensed, according to the review done in

1968. He asked for the exact figure. Mr. Staats stated that he could find out later for the record, but the study clearly showed that there was a failure of licensing for Government-held patents.

Dr. Siekevitz asked Mr. Staats his views on march-in rights and conditions set thereon. In Dr. Siekevitz' view, NIH needs to oversee patent administration through the IPAs to ensure that the rights are being used and licenses being granted. Mr. Staats agreed that there is a need for appropriate oversight and that judgments concerning march-in rights can be made on a case-by-case basis.

Mr. Hutt inquired how often the march-in rights provision has been used by Federal agencies. Mr. Staats stated that it has been used sparingly if at all, which was the legislative intent of the bill. Mr. Bremer said he does not believe NIH has ever used the march-in rights and commented that this provision is not the appropriate one for providing oversight--that the requirements through the IPAs, the annual reports to the Department concerning patents, and their exploitation are where the oversight is done.

Dr. Fredrickson raised the issue of commingling of Federal and private funds at the universities and how that would affect the allocation of patent rights under the new legislation. Mr. Staats responded that if there is significant Federal support, the law applies. Dr. Vagelos commented that, indeed, the law would stimulate increased support by industry to universities, tending to increase commingling of funds.

Dr. Sokol asked Mr. Staats' views concerning the question of recoupment, adding that he does not consider such a policy wise. Mr. Staats remarked that there was a provision on recoupment in the proposed legislation which was dropped from the bill as not being politically acceptable to the nonprofit institutions and small business organizations. Dr. Fredrickson noted that this issue had come up in NIH's briefing of President Reagan's transition team in December and that NIH has prepared a paper on the point. It would seem from the discussion and from the consideration of the legislation that the concept of recoupment is losing ground, and Mr. Staats agreed with that view. He brought up a different issue regarding recoupment: savings by agency managers who run a more efficient operation. Now there are no incentives because the only result is a budget cut, but if there could be some recoupment to the agency, managers might be encouraged to do their work more efficiently.

Mr. Hutt asked why the 1980 legislation did not extend to large corporations. Mr. Staats said that it was Congress's judgment that the bill would not pass with that provision--that it would be better to start with small business organizations and nonprofit institutions, and if the law was successful it could possibly be extended later. Mr. Hutt noted that small businesses and nonprofit institutions can go to large corporations for licensing, and Mr. Staats said that was correct. Dr. Fredrickson asked whether Federal laboratories would continue to be treated differently from university laboratories, and Mr. Staats said the law has not changed that; the rules here are basically those that have governed since 1950, preventing the Federal employee from owning the patent and the agency from licensing it. Dr. Fredrickson asked how commingling of funds of the Federal laboratories would be handled, and Mr. Staats said that would be a matter for the GAO lawyers to consider.

Finally, Dr. Siekevitz remarked that in his view a distinction should be made between patents granted to individuals or industry and those granted to government or government-supported investigators at universities. There is greater need in the latter case, he said, for public scrutiny and oversight. Mr. Staats noted that perspectives vary here and alluded again to the philosophical differences when the Commission on Procurement examined this in the '60s and '70s. But generally, he said, there is now a consensus, as reflected by the legislation, that these patents and licenses should be assigned in order to get the products into the marketplace and enhance our lagging national productivity.

HHS Patent Policies and Department Portfolio

Darrel J. Grinstead, Assistant General Counsel
Business and Administrative Law Division
Department of Health and Human Services

Mr. Grinstead summarized HHS policies and the current Department portfolio. (See Attachment E for background information to Mr. Grinstead's presentation.) Mr. Grinstead noted that there are 1,376 current patents for HHS, more than 600 of which have been assigned through IPAs. He noted that for a variety of reasons, there has been no thorough high-level Department review of patent policies. First, there has been disagreement within the Department on what should constitute patent policy, and further the Department has not acted because of long-pending legislation on patents that finally passed in the last session. With the Congress considering several measures, the Department decided it was best not to try to create an administrative policy at the time. The Patent and Trademark Law Amendments provide a statutory framework for patent policy, not only for the Department but for the entire Executive Branch.

Mr. Grinstead concluded his opening remarks with the comment that the Department has always had internal differences on the allocation of patent rights, ranging from whether the Government should dedicate patent rights to the public, retain the rights and license the invention, or allocate the rights to the inventor, grantee, or contractor for licensing. Now it is generally agreed that the Government should grant the patent rights to grantees or contractors for commercial development. That, basically, has been the policy of the Department in the use of IPAs, which are intended to facilitate movement of the invention into the marketplace, with the provision that if it is not marketed the Government has the march-in option to back the rights. For those institutions that do not have IPAs, the policy permits application for patent rights on a case-by-case basis. Mr. Grinstead said the Department has generally waived the rights to the petitioner.

He remarked that the Patent and Trademark Law Amendments will not change HHS policies, because, in effect, they extend the policies across the board through IPAs. Some Department rules will have to be changed because IPAs have not heretofore been granted to small business organizations and under the Act they will be. He noted that this law turns the question from who should own an invention to how can an invention best be developed and the technology transferred to the marketplace.

Mr. Grinstead outlined several cases illustrating issues that will continue under the Act, especially concerning march-in rights. He described a case that raised the question of how long a time is reasonable for licensing an invention and getting it to users. In 1968 a particular drug was invented and a patent issued. Patent in hand, the organization granted an exclusive license to manufacture, but FDA had not approved the products for marketing. However, a foreign company received FDA approval to market the drug in the United States, and the Department licensed the foreign manufacturer to provide drugs to Public Health Service facilities. So there is a dilemma as to whether the Department should use its march-in rights to take back title to the patent and try to license someone else who could get FDA approval more speedily.

Another case Mr. Grinstead cited involved the question whether march-in rights should be invoked in regard to a reasonable return on an invention. The Department is currently being petitioned by two manufacturers of a medical testing device developed under HHS support, with a patent granted to the university. According to the two companies, the university is asking exorbitant royalties, and the companies are petitioning the Department to take back the patent rights. Issues raised here are whether the clause should be invoked and whether HHS has the authority to be a royalty rate regulator. The Department is understandably loath to get into this particular area. Other circumstances arise for consideration. How should royalties be shared between the scientist-inventor and the institution? Presently conditions are set in the IPAs for allocation of royalties to the scientist and to the university. There might be a misuse of the royalty rate structure if universities were to vie for scientists by offering them a higher percentage of the royalties. Other issues that have been raised are whether granting exclusive rights to an institution can compare with the possibility of developing an invention by competitive procedures through the contract process. These important issues remain under the new legislation and will require the attention of the Department.

Committee Discussion

Dr. Margery W. Shaw
Director, Medical Genetics Center
Graduate School of Biomedical Sciences
University of Texas Health Science Center at Houston

Dr. Shaw, commenting on Mr. Grinstead's remarks, noted that in reviewing the briefing material for the meeting she was relieved to learn that the patent process, as Chief Judge Markey stated, facilitates rather than hinders information exchange. She added that a number of questions from the area of recombinant DNA research had come to her mind concerning patenting. For example, Chakrabarty was from General Electric, but much of the work in this area had been done by university scientists like Hamilton Smith, the Nobel Prize winner who discovered the restriction endonucleases, the enzymes essential for recombinant DNA technology. She went on to question whether, through this technology, the development of gene sequences would be patentable, and she also noted the recent Supreme Court decision stating that computer programs are patentable. She stated that the Chakrabarty decision has enormous impact for biomedical research, and added that the impact would be far greater on health research and NIH than on any other research area. Thus she believes that this meeting is very timely, for clearly these will be key policy issues for NIH in the next decade.

Dr. Warren B. Cheston
Associate Director for Administration
Wistar Institute

Dr. Cheston spoke from his perspective as the Associate Director for Administration at the Wistar Institute, adding that the Institute is private and small in comparison with most of the grantee institutions of NIH, with approximately 100 professional employees and a budget of $15 million annually. The IPA with the Department has been essential to the operation of the Institute, which receives a large portion of its funds from NIH. Royalty income constituted 6 percent of the 1979 budget and is expected to account for 10 percent of the 1985 budget. This income is essential, since the Institute has few sources of funds to supplement grants--no students, alumni, or patients, as have universities and health care centers.
Dr. Cheston noted that Wistar has six U.S. patents, five of which have been licensed; one corporate research agreement, with first option to the corporation; and finally, seven patent applications pending. Dr. Cheston cited two license agreements that provide income to his institute: a rubella vaccine marketed in the United States by Merck and a human rabies vaccine developed in 1979.

Dr. Cheston strongly endorsed the concept of the IPA as described by Mr. Grinstead. He commented that it sets the ground rules for the licensing agreement and provides a clear statement of the restrictions, if any, imposed by government funding of the research leading to the invention to be licensed. He added that march-in rights had to be real and not merely an administrative device with no possibility of being used. He felt that a licensee must know that the license may be revoked if the licensee does not perform in the public interest. He also commented on Mr. Grinstead's example of the specter of excess profiteering by the university. He noted that profit is an inappropriate term to apply to earned royalties; royalties on an invention rarely repay the institution's investment in the research as a supplement to NIH funding. For example, development of the rabies vaccine took 25 years, during which Wistar provided significant funding from its own resources. He added that institutional governing boards need to have a far better grasp of the issues involved in technology transfer and that reasonable guidelines in equity should be available for all parties concerned, as suggested by Chief Judge Markey. Dr. Fredrickson commented that under the Patent and Trademark Law Amendments, the Government, and therefore the Department, apparently would not specify conditions for the royalty rates to be shared between the inventor and the institution.

Howard W. Bremer
Patent Counsel
Wisconsin Alumni Research Foundation

Mr. Bremer provided perspectives from the Wisconsin Alumni Research Foundation, which was created in 1925 as an autonomous and independent patent agency for the University of Wisconsin. He said that this foundation has been especially aggressive in patenting inventions--that it holds 121 of the 604 HHS patents given to institutions. He noted that the foundation has assumed the costs of handling these inventions--approximately $800,000 in fees for patent filing in the United States and other countries, not including the administrative costs to the foundation. He stated that income from foreign sources is actually more than that from U.S. companies, especially drug companies. There is a disparity because FDA regulations make production more costly for U.S. drug firms, whereas foreign companies can get faster approval for marketing drugs in their countries. Moreover, the FDA rules to ensure safety and efficacy reduce the time of exclusivity of the patent use and licensing. Mr. Bremer noted that because of the cost involved, it is not easy to get companies to take the patents. It has been estimated that 10.7 times the dollars spent for research are required to bring a drug to the marketplace. Mr. Bremer referred to the discussions of Chief Judge Markey and Drs. Vagelos and Sokol concerning restoration bills in the Congress to provide relief here. He noted that the Patent and Trademark Law Amendments do toll the time of exclusivity while regulatory agency action is pending, and this is a step in the right direction.

Mr. Bremer reiterated Judge Markey's comment that a patent is really the right to exclude, and that IPAs provide this right to the universities. They assist in facilitating technology transfer. Before 1968, the Government could not transfer invention rights to the university. After the 1968 GAO recommendations and the institution of IPAs with HEW, there was a marked difference in getting the inventions out.

Mr. Bremer emphasized Judge Markey's comment that technology is the currency of international trade. He cited the Judge's statistics about loss of our position in international trade, with our competitors filing patent applications and using many of our inventions to our disadvantage. On the issue of march-in rights, Mr. Bremer shared Judge Markey's concern that an invention may be a "late bloomer." He cited the development of the thermoluminescent dosimeter (TLD). Not until nine years after the patent was issued did the state of the art catch up so that TLD could be used successfully.

Concerning the issue of recapture of royalties by NIH, Mr. Bremer said that there had been a payback provision in S.414, but it was removed in the legislation that ultimately passed. The provision would have provided payback for the NIH investment, which, after all, would be very difficult to do. Further, Mr. Bremer emphasized Dr. Cheston's comments that the issue here is not profits on the license, but one of royalty return. Without Mr. Bremer's foundation, for example, many of these inventions would never have gotten into the marketplace. It is the royalty returns that keep the foundation and the university ultimately successful in developing inventions.

Clearly, in the foundation's experience, there are corporations that would take a license for an invention from his foundation that would not take one from the Government. He cited examples to illustrate this point. He noted that royalties received by the university can be returned directly to R&D, which would not be the case if the Government held the patent and issued the license.

Licensing, Mr. Bremer said, is an effective and efficient mechanism for getting technology into the market and for getting returns on an investment to finance further R&D at the university. He also pointed out that the returns should be proportional to the risk. It generally costs $12 to $15 million to develop to the clinical stage a new chemical entity for pharmaceutical use. This does not include the cost of the clinical trials; nor does it include the cost of marketing, which had been cited before as about 10.7 times the original investment. Under the present IPA agreement, industry, Government, and the university all benefit. Clearly, with income being generated under a patent agreement, NIH will need to provide less money, or at least, in a sense, there will be more money for research at the university level.

Finally, Mr. Bremer commented on Mr. Grinstead's point that petitioners to the Department had charged that the universities were asking too much for royalties and requesting that nonexclusive licenses be granted. It is easy, he said, to suggest this, once the feasibility of an invention has been shown and one can piggyback on all that original investment. The issue of reasonable royalty rates is especially difficult. There could be an avalanche of cases if the Department got into this, and it would be best avoided, if at all possible.

Dr. Fredrickson asked Mr. Bremer whether there were organizations similar to his at other universities. Mr. Bremer replied that there are several different administrative mechanisms at universities to handle patents--patent offices, research corporations, and the like. He stated that his foundation is unique in its autonomy and acts as an agent only for the University of Wisconsin.

Future Directions Under Public Law 96-517 (Patent and Trademark Law Amendments) and Public Law 96-480 (Technology Innovation Act of 1980)

Melvin S. Day, Director
National Technical Information Service

Mr. Day commented that Mr. Staats had given an excellent historical perspective on developments leading to the passage of the Patent and Trademark Law

Amendments and that Mr. Grinstead had provided a good view of the Department's policies and how the new law would affect them. (See Attachment F for section-by-section analysis of the Patent and Trademark Amendment Act of 1980 (P.L. 96-517)and the Technology Innovation Act of 1980 (P.L. 96-480).) Mr. Day briefly described the operation of the National Technical Information Service (NTIS). He explained that NTIS is the agency through which other Federal agencies promote and license their patents. He also noted that Public Law 96-517 will stimulate Federal efforts for technology transfer to the private sector. The law provides incentives by allocating patent rights to nonprofit institutions and small business organizations and removes a number of obstacles that have been there in the past. Mr. Day added that Federal patents representing an investment of $10 million have been licensed. It is estimated that by 1986 about $1 million in royalties on these licenses will be returned to the Government each year.

Under the new law, exclusive licenses are limited to the earlier of two dates--5 years from the first commercial use or 8 years from the date of license. Mr. Day remarked that there is probably a need for longer-term exclusive licenses for the reasons covered by Chief Judge Markey. The law does, however, permit greater flexibility for licensing of Federal patents and provides protection for proprietary information. Federal property management regulations currently restrict patenting and licensing of inventions developed in Federal research laboratories, such as those at NIH. The regulations are being revised in light of the new law to provide greater flexibility in regard to small businesses and nonprofit organizations.

The law does place certain requirements on patenting. There are sections having a preference for U.S. industry--namely, that under exclusive licenses any products embodying inventions must be manufactured substantially in this country, with agency approval required for exceptions. Mr. Day noted that this restriction was applied by the NTIS even before the statutory mandate. There are other general requirements--none of them onerous, he added--for reporting inventions, electing rights, and following patent applications. Additional provisions allow for reexamination of patents by the Patent Office, which would permit challenges to patents there rather than by litigation, as at present. Further, there are sections on administration fee-setting and on certain copyrights for computer programs. Mr. Day characterized this as an important Act that should substantially promote the transfer of Federal R&D inventions into the private sector and meet many of the challenges cited by Judge Markey and Mr. Staats.

Committee Discussion

Peter Barton Hutt
Attorney-at-Law
Covington & Burling

Mr. Hutt said that in the 1960s several drug firms that were clients came to ask his firm's advice on their posture regarding the licensing of inventions developed under Federal support. At that time his firm advised companies that they should not consider licensing any drugs that had been developed under Federal support in part or in whole because of the lack of statutory framework and conflicting administrative policies from one Department to another. Mr. Hutt noted that the new law has changed the situation somewhat. However, he pointed out that there are still defects from his point of view. One, the law is limited to nonprofit and small business organizations and does not extend to large corporations, primarily for political considerations, as Mr. Staats indicated. Mr. Hutt suggested that we might consider a mechanism like the IPA for the large corporation or business. It might be called a business patent agreement (BPA). This would provide for direct Government-industry arrangements, rather than the present situation wherein industry deals with the universities, which deal with the Government. He pointed out that barriers are still erected around the use of licenses, particularly their exclusive use. He noted that this conflict is very important because business basically needs certainty and protection for its enormous investment. He added that the Office of the General Counsel's 1978 review of institutional patent agreements renewed the uncertainty about administration of the IPAs and about HHS's posture toward the allocation of patent rights to the universities with licensing in the private sector.

Mr. Hutt continued that the status of the Department's review of the IPA policies is not clear, but that, in any case, the law will now set a statutory framework for policies in effect before the review began in 1978. So again, some of the questions have been solved by the Act, but it still does not solve the problem for the large corporations. He urged consideration within the Department for a business patent agreement.

Concerning the question of march-in rights and exclusivity, Mr. Hutt noted that he had just been told that agencies have invoked the provision--that NASA, for example, had exercised march-in rights over 100 times, but without opposition. This, in effect, was a "voluntary" relinquishing of the patent rights involved under the threat of a formal proceeding. (Mr. Staats had asked the relevant GAO officials to make a quick survey of the agencies and had reported that there is no record of the exercise of march-in rights actually resulting in the patent rights reverting to the Government.) Mr. Hutt cited the cases provided by Mr. Grinstead as ones that cause a great deal of concern to industry, especially if the Department can have authority to consider march-in rights on the basis of these examples.

Mr. Hutt expressed his lack of enthusiasm for the Stevenson-Wydler Act. In his view much of what the bill is trying to accomplish can be done more reasonably by the private sector than the Government. The more important aspects here are those of the Patent Right Bill, under which the Federal Government could better facilitate technology transfer.

Arthur R. Whale
General Patent Counsel
  and Assistant Secretary
Eli Lilly and Company

Mr. Whale opened by noting the importance of this meeting in bringing together representatives from industry, university, and government to discuss how better to support health research and to facilitate technology transfer. In commenting on the Patent and Trademark Law Amendments, he reemphasized that big business, as Mr. Staats and Mr. Hutt had noted, was excluded principally for political reasons--that clearly there was no logical reason to exclude large corporations from the application of this Act, especially if it was passed to facilitate technology transfer. Thus, the bill does not set a uniform policy, but in effect sets up two policies, one for small businesses and nonprofit organizations and one for other organizations. This is not a distinction that can hold. Thus, the law is an important beginning, but it really should be extended to all corporations. Mr. Whale commented on the previous discussion concerning the march-in rights provision, remarking that it casts a cloud on the title of patents and is therefore of concern to industry. He said he hopes the Federal management procurement regulations, noted by Mr. Day, reflect the spirit of the law, because a number of subjective interpretations are possible that might result in unnecessary barriers. The law also sets up an oversight responsibility concerning implementation that, logically, should be in the Department of Commerce.

Mr. Whale noted that there are 29,000 Government patents and only 4 percent are licensed. One might ask why there are so many. The answer is that the Government must frequently patent defensively, but one alternative might be just to publish the results in the literature. It would be wise to consider different patenting policies here, because there is cost associated with these patents. Maintenance fees alone could amount to $800,000 per year, so there is need to consider some restraint.

Mr. Whale also endorsed the patent term restoration bills before Congress for extending, especially in the drug area, the period of patents for the time consumed by regulatory review. He pointed out one problem with the recently passed amendments to the patent law--namely, that the licensing organizations may be required to report to Federal agencies on efforts to commercialize an agency-funded invention. The issue here, once again, is loss of trade secrets and proprietary information. There is no protection in the Act; the language is permissive, using may rather than shall regarding protection against availability under the Freedom of Information Act. Finally, the Act, by its very nature, sets up a distinction in licenses to small business organizations and large corporations, in severely limiting exclusivity for the latter.

Mr. Whale noted an earlier comment that patenting could inhibit free and early interchange between scientists. He thought that a more likely source of inhibition was the new patent law amendment requiring small business contractors of nonprofit organizations to share royalties with the inventor.

Dr. Jack T. Sanderson
Assistant Director for
  Engineering and Applied Science
National Science Foundation

Dr. Sanderson of the National Science Foundation remarked that NSF has been promoting many of the policies and recommendations being discussed at this meeting. In effect, the Act setting up NSF gives it the right to dispose of Government property, and NSF has interpreted this mandate to apply to patents that merit allocation to its grantees. Dr. Sanderson stressed the need for these policies, especially in view of the relatively high cost of licensing and marketing. NSF has used the IPA with success. Essentially the agency has been out of the patent business; it owns no patents. Under an NSF experimental program intended as an incentive to development, patent rights, through prenegotiated agreements, would go to small business organizations, but only after the company has obtained venture capital equivalent to the original NSF investment. This program will be eliminated under the new law. Thus, the law limits some of the flexibility that NSF has had in the past.

First Day: Afternoon Session

II. NIH RESEARCH RELATIONSHIPS WITH EDUCATIONAL INSTITUTIONS AND INDUSTRY

National Institute of Allergy and Infectious Diseases: The Hepatitis B Story

Dr. Richard M. Krause, Director
National Institute of Allergy and Infectious Diseases
(with Drs. Harvey J. Alter and Robert H. Purcell)

Dr. Krause opened by stating that he and Drs. Alter and Purcell would summarize the material provided to the Committee members and participants before the meeting. (See Attachment G.) Dr. Krause related that basic research had laid the groundwork for the development of the hepatitis vaccine. Once the breakthroughs occurred, there was splendid Government/industry /university cooperation in bringing the vaccine to fruition, making a remarkable story.

Approximately 150,000 people per year were affected by hepatitis B as recently as 1975, Dr. Krause said. He went on to review briefly the nature and types of acute viral hepatitis and summarized the Government support that led to the commercial development of a hepatitis B vaccine. All told, approximately $6.7 million was committed in 1972 and $9.8 million in 1980, with the largest proportion of support coming from NIH. From this research came the diagnostic blood test for detecting hepatitis B and also the development of the hepatitis B vaccine. Through use of the diagnostic test, post-transfusion hepatitis B has fallen dramatically. There is still a potential need for the hepatitis B vaccine to reduce the morbidity and mortality of 150,000 cases per year in the population at risk.

Dr. Alter summarized the basic research discoveries that led to the development of the diagnostic test, beginning in 1963 at NIH with Dr. Blumberg's work on the Australia antigen. Within six years, that discovery led to its application to detect carriers of the hepatitis B virus and to routine hepatitis B antigen testing of blood donors. Within 15 years this antigen became the basis of a highly effective vaccine. These truly remarkable technological developments followed the serendipitous discovery of the Australia antigen, the demonstration of its association with leukemia and Down's syndrome, the demonstration of its infectious origin, and finally, documentation of its link to viral hepatitis. Research is now proceeding on developing a diagnostic test for the non A-non B (NANB) virus, which currently causes approximately 98 percent of post-transfusion hepatitis cases each year.

Dr. Purcell described Dr. Saul Krugman's important role in initial discoveries. He went on to explain research with animal models, Dr. Norman Anderson's development of the ultracentrifuge technique, the clinical trials in homosexuals, and the preparation of the vaccine. There is now a strategy to prepare pure vaccine using a variety of techniques, including recombinant DNA. Some hurdles to confront are the problems of residual live virus, secondary responses to the vaccine (such as an autoimmune phenomenon), or idiosyncratic responses (such as the Guillain-Barré syndrome). The status report is that Government/university/industry cooperation will yield a vaccine to prevent and control type B hepatitis.

Committee Discussion

Dr. Fredrickson commented on the superb report of Drs. Krause, Alter, and Purcell. The elegance of the work and the speed at which the technology is moving, Dr. Fredrickson noted, are really quite extraordinary, and a testimonial to scientific process at its best involving Government, universities, and industry.

Dr. Samuel O. Thier
David Paige Smith Professor
of Medicine and Chairman
Department of Internal Medicine
Yale University Medical School

Dr. Thier, following up on Dr. Fredrickson's comments, noted that the description of this research and the arrangements among all the parties suggest a system of loops and feedback that may make it a unique experiment approaching the ideal. Thus, it may not be an applicable model for other research areas, particularly in the rapidity with which the basic research results led to commercial applications.

Nevertheless, Dr. Thier pointed out, there are a number of lessons to be taken from this description. First, basic research, as exemplified in NIH investigator-initiated research grants, is not well suited for industrial support because investors are reluctant to risk a lot of money where the outcome, and therefore the possible profits, may be far in the future. Thus, the role is clear at basic levels for the Federal Government and the universities. Second, once the basic research has been done, one must consider the next steps of development--and here effective interfaces between government, universities, and industry are critical. All three will have played respective roles in successful outcomes. Finally, development is predominantly an industry activity, and government and universities should ordinarily not stray into this area.

Dr. Thier noted that certain issues need to be considered. What is the industrial role in support of research, especially in terms of risk and profits from development? Is the industrial role applicable to support basic investigation at universities? Especially critical is determination of the relationships among Government, universities, and industry with respect to the nature and support of research. For example, there might be some mechanism whereby industry can support basic research at universities and have the patent rights and licensing for development, with some possibility of royalty return or some portion of the profits plowed back into the universities for more basic research.

Dr. Maurice R. Hilleman
Senior Vice President
Virus and Cell Biology Research
Merck Sharp & Dohme Research Laboratories

Dr. Hilleman, of Merck, in commenting on the presentations, noted that the Government played a dominant role in the development of hepatitis B vaccine. The industry's role, particularly at Merck, has been to focus efforts on the development of a safe, effective vaccine that is as pure as possible. These efforts began in 1968 with the development of antigen purification. In 1975 human tests began, using 17 lots of vaccine, with more than 5,000 people tested. Manufacture started in March, and Merck hopes to market the vaccine in 1982. Further, there is a possibility for world markets. Merck is using recombinant DNA techniques and has pioneered in the development of a vaccine for hepatitis A. A lot more research is being done at Merck, and Dr. Hilleman commented that the cooperation between Government and industry in this area has been splendid, as evinced by Dr. Krause's presentation.

Dr. P. Roy Vagelos
President
Merck Sharp & Dohme Research Laboratories

Dr. Vagelos remarked that a number of key policy questions are subsumed under these cooperative arrangements. One is the question of liability for the company making vaccines, and he urged that there be more consideration for Federal support of public immunization programs and the question of industry's liability. Merck's position is that they do not need such Federal underwriting for their work with the private physician, where there is sufficient opportunity for informed consent; but in the passive public immunization programs, where consent cannot be obtained as explicitly, Merck seeks some Federal protection or indemnification. He voiced strong support for the Centers for Disease Control, especially in its efforts to monitor infectious disease and to implement public vaccine programs. In fact, 70 percent of the pediatric vaccines of Merck are supported through CDC's public immunization programs.

Dr. Vagelos also raised the matter of vaccines for various targeted populations. He believes that vaccines for children are reaching intended populations to control diseases reasonably well. That, however, is not the case with adults; and he used as an example the pneumococcal vaccine. Thus, for adults there should be more effort, through CDC and other Federal agencies, to provide necessary public information on these vaccines and their availability.

Finally, Dr. Vagelos spoke briefly concerning the relationship of the Government, industry, and the universities. He agreed with Dr. Thier that the appropriate split is for basic research to be done by the Government and the universities and for industry to do the developmental research and marketing. The Government should not develop vaccines, especially those that could be used on large populations where there is incentive for industry to produce and market them. In the area of what might be called "orphan vaccines," such as meningococcal, there may be more of a Federal role. Clearly, there is a Federal role for support of clinical trials for vaccines. Indeed, CDC has been especially helpful in supporting and conducting trials for Merck vaccines. He strongly supported Government involvement here.

Dr. Walsh McDermott
Special Advisor to the President
Robert Wood Johnson Foundation

Dr. McDermott echoed a previous speaker's comments about the elegance of the research and cooperation in the development of the hepatitis B vaccine. He raised the question of how this all came together. Who got the various scientists and appropriate officials from so many different institutions to mix so well and get this basic research and technology linked and moving so quickly? In his perspective, the interaction among the systems is fascinating, and one may ask to what extent this model could be applied in the next decade to address the issues raised at this meeting. He suspects, as does Dr. Thier, that what was described is an ideal model, because this is an area of research and development for which cooperation is absolutely essential. All parties need each other in order to develop vaccines. But this model may be an ideal rather than a prototype. It does reveal that the system was not laissez faire--that someone had to bring the results to the attention of relevant people in government, industry, and universities.

Dr. McDermott suggested that some institutional channel be created to bring together the marketplace of ideas and the marketplace of commerce in many research areas. What is needed is some gentle direction; someone needs to play the role of convener. Dr. McDermott suggested that perhaps NIH, through its consensus meetings and the Office of Medical Applications of Research, might provide such an institutional focus. Currently the consensus meetings focus more on which is the better of two treatments, whereas he proposes a group that might meet periodically to look at the chain of events in pathogenesis. They would point out where there are weak links and which organizations--government, industry, or universities--might assist in providing a breakthrough or forging a new link. Clearly, this could not be done, he said, in just one meeting, but perhaps there could be some ongoing forum over months or years that could monitor progress and try to promote the kind of feedback loops demonstrated in the hepatitis B story.

Finally, Dr. McDermott pointed out that biomedical research is different from other scientific disciplines. Research, he explained, is directed to the discovery of a cure, and once a cure is found--for tuberculosis, say--the scientists and scientific community move on to the next hurdle. The practice is not to go back to the original discovery and see whether it can be done more efficiently or more cheaply; that clearly is the role for industry, as distinguished from government or university research.

Dr. Vagelos concluded the discussion by citing the important support of the National Institute of Allergy and Infectious Diseases for clinical trials of the hepatitis vaccine. Echoing comments of Dr. McDermott, he added that it might be useful to try to convene all concerned parties to decide what to do next if one could get a consensus about the priorities or relative importance of particular vaccines and populations. It certainly would assist both government, university, and industry on approaches to attack the various research problems. Dr. Krause said that indeed the Institute of Medicine will be working with his Institute and companies like Merck to attempt to begin tackling this very problem. Dr. Fred Robbins, the new President of the Institute of Medicine, will take a lead effort in this regard.

National Cancer Institute Research Program

Dr. Vincent T. DeVita, Director
National Cancer Institute
(with Dr. Saul Schepartz)

Dr. DeVita opened by presenting an overview of the National Cancer Institute, its budgets, and programs. (See Attachment H for relevant documentation.) He noted that there are approximately 1.2 million cancer patients, with approximately 200,000 receiving some form of chemotherapeutic treatment. Because there are so many different cancers, drug treatments cannot compare with the magnitude of the vaccine programs, though the patients are numbered in the thousands. Thus, these are "orphan" drugs.

Dr. DeVita provided a brief history of the treatment programs of NCI. The Institute's extramural chemotherapy program began in 1955, and in 1957 NCI began its R&D contract program with industry in the development of anticancer drugs. By 1970, 12 cancers were curable with drugs. In 1979 sales of anticancer drugs totaled approximately $140 million, and of that, approximately $35 million was spent for one drug, adriamycin. Over half of the $140 million was spent for drugs having sales in the range of $1 million or less per year. For each drug developed, there is an investment of $50 to $70 million. Therefore, NCI's involvement in drug screening and development derives from the fact that returns can rarely equal the original investment.

Dr. DeVita noted that the program of the NCI in 1976 got out of the synthesis of analogs of active drugs. It was felt that industry could take this over without need for an excessive investment. Right now the Cancer Institute is considering how to get the private sector to become more involved in the chemotherapy program, particularly in the preclinical development of new drugs. The key roadblock is developing cheaper methods for toxicology testing. If such methods could be found, industry and even universities could assume much of what is being done by the Cancer Institute, so the Institute is focusing on research to find cheaper methods. The anticancer drug development program, funded at $36 million in 1976, was down to $31 million in 1980. The basic drop is because of elimination of exploratory research on the discovery of drug analogs. Dr. DeVita concluded by pointing out that the cancer budget for 1980 was $999 million, and approximately 32 percent of that was devoted to cancer treatment--27 percent in the Division of Cancer Treatment. All told, approximately $120 million was spent in 1980 for clinical trials.

Dr. Saul Schepartz followed Dr. DeVita's opening comments with a review of the NCI drug development program and examples of the NCI program that illustrate the Government/university/industry roles in this area. (See Attachment H for Dr. Schepartz's prepared remarks and background on the drug development program. Also included is a summary of the orphan drug bill (H.R.1663).) Dr. Schepartz briefly described the history of four drugs, the first three of which are currently on the market, that serve to illustrate the many different relationships between the Cancer Institute, universities, and industry. He cited the drugs (1) mithramycin, (2) cytosine Arabinoside, (3) cis-platinum, and (4) AZQ. These four drugs provide examples of the following: (1) alternate patent clause applying to drugs developed under R&D contracts with the pharmaceutical industry, (2) an industry-discovered compound developed largely by the Government, (3) a compound discovered in a university and owned by it under an institutional patent agreement, and (4) an intramural Government discovery.

Committee Discussion

Dr. Irwin H. Lepow
President
Sterling-Winthrop Research Institute

Dr. Lepow noted that he has been in industry for only the past two and a half years; before that his career was exclusively at the university. However, he has had a long association with patent policies involving universities. He began his training and initial academic work at Western Reserve University in a laboratory headed by Dr. Pillemer, where the DPT vaccines were developed and patents and licensing led to industry. He saw early on the kinds of relationships that could be developed, are now being discussed at this meeting, and were discussed and reviewed by Dr. Krause and his colleagues from the Allergy and Infectious Diseases Institute.

Dr. Lepow noted that the key issue for supporting patents is that they protect one's investment. He noted that in 1978 industries expended approximately $1.4 billion for R&D; in 1979, $1.7 billion; and in 1980, $2.0 billion. The pharmaceutical industry commits approximately 11.5 percent of ethical drug sales to R&D. Thus, it is a research-intensive industry. In order to demonstrate the amount of investment and the return, Dr. Lepow stated that 23 new prescription drugs were released on the market in 1978. If one considers the R&D investment by industry in 1978 as $1.4 billion, then roughly $61 million was spent in research for each new drug entity on the market.

Dr. Lepow quickly noted that this is clearly not the whole story--that R&D budgets go for many other purposes, such as research on over-the-counter drugs and the like--but it does provide some sense or measure of the ratio of investment to return. Thus, the patent, and especially the patent life of 17 years, is vital to the drug industry, providing the support for new drug development.

He cited as an example of industry contributions an article by Irvine Page in the New England Journal of Medicine, March 5, 1981, crediting the antihypertensive drugs to the industrial chemists. Dr. Lepow noted that industry does support orphan drug development in some areas. His own company has two such drugs in development, one for the treatment of hereditary angioneurotic edema, which affects about 10,000 people, and the second for the treatment of Cushing's and Conn's diseases. However, the role of the Cancer Institute is particularly important, and their drug development program is a good model, especially with respect to the working relationship with industry and the patent protection for industry.

Mr. Hutt asked whether the alternative patent clause, as described by Dr. Schepartz, which permits industry to retain the patent, is not in effect equivalent to what he was advocating earlier in the form of a business patent agreement. In fact, the NCI's program permits free-standing contracts with the pharmaceutical industry with patent rights vested in the industry but subject to march-in. Thus, Mr. Hutt concluded, the Department could, if it wished, create business patent agreements administratively, based on the NCI model. Dr. Schepartz noted that other Institutes had requested a policy comparable to that of the Cancer Institute but that the Department had declined to approve such an arrangement. Mr. Hutt reemphasized that it is a question of policy and not of law--that it would seem to be clear that the law would not prohibit it and the Department would therefore have the discretion to do it.

Mr. Hutt also asked the Institute's role regarding moving new drug applications (NDAs) at the FDA. Does the Institute, as part of its drug development program, also deal with the FDA in the initial stages of processing NDAs? Dr. DeVita responded that the Institute always files for an investigational new drug application (IND), but it has not proceeded to apply for

NDAs. That has been the responsibility of industry. There was one case, however, in the development of a drug for adrenal cancer, where the patient population was only 600, in which the Institute did most of the staff work in preparing for the NDA that was ultimately submitted by the licensee. In addition, as part of its program in the Phase II testing where some of the results are coming out and many people want access to the drug, there is a procedure at the NCI for such drugs (entitled "Group C") that in effect is a request of the FDA for a "compassionate IND." Here the FDA will permit use of the drug for the selected cancer population. Mr. Hutt concluded that this is a very important issue: Who files and moves for the NDA, assuring a willingness to take on some of these drugs?

Dr. Temin asked whether any of the profits from the drugs on the market have been returned to the NCI by the pharmaceutical industry. Dr. DeVita responded that it has not been the policy of the Institute to request royalty returns on the patents, pointing out again that for most of the drugs the sales are in the neighborhood of $1 million and that it has not seemed worthwhile to try to create procedures to recoup some of the funds. But, he added, the market has expanded over the past 10 years as more effective drugs have become available, so the Cancer Institute could consider some form of payback on its investment. It has not done so, largely for administrative or policy reasons.

Dr. Temin noted that during the discussion a number of questions had been raised about the appropriate role of NIH and the universities, with a commitment to basic research, and of industry, with its commitment to applied and developmental research. Dr. Temin pointed out the new phenomenon of molecular biologists at the universities forming their own corporations, and the muddying of boundaries as the university researcher joins business ventures. Dr. Temin was especially concerned about the long-term aspect of this phenomenon, particularly as regards basic research at the universities. He concluded his comments with the view that there appears to be a real conflict of interest for the professor who is also a businessman, particularly in the engineering area. In response to a question, Dr. Fredrickson noted that the drug development program at the NCI is the only one actively involved in orphan drugs and that quite frankly, it is a luxury; that the NIH could not propose this across the board for all its Institutes, especially in view of the constrained budgets.

III. INDUSTRY SUPPORT FOR HEALTH RESEARCH

Venture Capital and Industrial Investment in the Development of Health Inventions: Respective Roles of Industry and Government

Dr. Irwin H. Lepow
President
Sterling-Winthrop Research Institute

Dr. Lepow commented that the academic and industrial research communities are two different worlds. The process of the research is the same, but the goals are different. The purpose of government and university research is to expand the frontiers of knowledge, while that of industry, particularly pharmaceuticals, is to develop new products and earn profits on the investment. Dr. Lepow commented that Dr. Krause and his colleagues had beautifully described the interaction among Government, university, and industry and their respective research roles along the research spectrum and into the marketplace. He emphasized the key role of the National Institutes of Health in this partnership and the need for a strongly supported NIH which ensures the science base and training for the Nation in biomedical research. He believed that more thought had to be given to developing the industry/university relationships as described and discussed throughout the meeting.

Dr. Herman Sokol
President
Bristol-Myers Company

Dr. Sokol summarized his paper which had been provided to the Committee members. (See Attachment I for Dr. Sokol's paper and data on health R&D funds used by industry and universities.) Dr. Sokol highlighted the pharmaceutical industry's research efforts, describing the industry as a key system and place for developing new drugs and vaccines and for proving the safety and efficacy of new drugs to satisfy the requirements of regulatory agencies throughout the world. In looking to the future, Dr. Sokol urged reexamination of the support for health research, noting that a greater percentage of basic research should be goal-oriented. He urged that industry be able to participate more fully in research study meetings between NIH and universities. He endorsed much of the Federal policy to encourage industry to commercialize important new Federally funded discoveries and made a number of recommendations concerning the patent system which in his view would encourage industrial development in several ways.

Belmont Towbin
L. F. Rothschild, Unterberg, Towbin

Mr. Towbin provided perspectives on venture capital in support of health R&D. He noted that venture capital can serve as a catalyst in the interface between basic research discoveries and development and commercialization.

In effect, it can assist research on the road to the development of the product. He then went on to describe venture capital, or speculative capital, which is used generally in two ways: (1) as seed money to assist an entrepreneur to start up and (2) to provide money for development after the entrepreneur has persuaded investors to exploit the invention.

Mr. Towbin went on to describe the phenomenon of venture capital over the past 30 years. He noted that after World War II only small amounts of venture capital were available. He mentioned Professor Dorio of the Harvard Business School, who promoted venture capital in support of science and technology through the American Research and Development Corporation. By this avenue funds were put into a host of technological developments, including heart pacemakers and digital equipment The sources for venture capital at that time were largely the wealthy families, such as the Rockefellers. However, as technology became more successful and offered the opportunity for greater payoffs, more money was enticed into the market from a variety of sources, especially with the spectacular development of such companies as Xerox and Texas Instruments. The phenomenon that has captured public attention today in the venture capital market is the recombinant DNA technology firms. Both Genentech and Cetus have attracted funding from major corporations, including Exxon and the like. Indeed, Cetus last week raised $100 million. He noted that this phenomenon has made people like Swanson and Boyer multimillionaires.

Mr. Towbin gave other examples of significant technological breakthroughs that brought the inventors enormous amounts of capital and wealth, such as Apple Computers, with each of the four original partners now worth approximately $200 million. He noted that in light of the cases he has described, one might say that a driving force behind venture capital, even though the risk is great, is the "hope of riches beyond the wildest dreams of avarice." Accordingly, venture capital generally cannot be used to support fundamental research, as it calls for a return within 3 to 5 years with a possibility of doubling or tripling the original investment. It is better suited to applied and developmental research.

Committee Discussion

Dr. Siekevitz asked whether, given the description of venture capital investment, it may not skew all the capital available for more long-term research because of the demands for higher returns in a short period of time. Mr. Towbin noted that corporations like the drug houses described by Dr. Sokol and others looked upon investments differently from the venture capital firms. Indeed, he added that Exxon is making major commitments to support basic research. Dr. Temin, citing Dr. Donald Kennedy, President of Stanford University, said that we have the new phenomenon of venture capital being invested in recombinant DNA firms that may be far from production. Professors are making enormous sums of money, even before a product is turned out; and this may have a deleterious effect on their commitments to research and on the university. Mr. Towbin responded that the emphasis in venture capital is on applications of technology, and it is recombinant DNA technology that is expected to pay off. The companies and the scientists involved are believed to be honest; they do not promise immediate payoffs, but the potential is there.

Dr. Andrews cited two cases in his experience that show the problems of venture capital investment in research as opposed to industrial investment, such as that of drug companies and chemical companies. Purdue offered a particular process to several corporations, but they did not believe it had much promise. However, the venture capital firm, having heard by word of mouth that the process would be used by the company and be highly profitable, invested anyway. The process has not yet been demonstrated to be commercially successful. Purdue asked that its name be removed from a prospectus for the sale of stock, since it appeared to be an endorsement. The University believes that it has a responsibility to protect potential investors who might make financial commitments on the strength of the University's name. Thus, Dr. Andrews prefers to have established corporations for support, such as drug or chemical companies, rather than venture capital companies. Mr. Towbin acknowledged that there are differences, but reiterated his belief that venture capitalists play an important and legitimate role in those areas of technology where the risks are greater and the large companies do not wish to put their funds.

Dr. Siekevitz remarked to Dr. Fredrickson that it seems clear, in light of the discussion, that NIH does not have a general policy to cover the questions raised. He asked what the NIH policies were regarding government, university, and industry relationships. Dr. Fredrickson said that Dr. Siekevitz had correctly noted that there are many policies and that this is why the meeting was being held--to air them, to find people's perspectives, and to decide what changes, if any, need to be made. But there is no one comprehensive policy, and there probably never will be or should be.

Mrs. Wexler said that a major point addressed at this meeting is the issue of creating wealth, and Mr. Towbin's examples of spectacular wealth being created in some areas of science are noteworthy.

Dr. McDermott remarked that the universities should consider establishing a code of practice for scientists. He added that problems for medical schools are different from other scientific schools and universities generally, because medical schools have income from patient care services that provide increasing support, though often at the expense of the research and education effort. He suggested that perhaps what is needed is renewed emphasis on teaching and research, which will always require certain sacrifices.

Dr. Fredrickson noted that two problems are highlighted--the possible harmful effects of some of these events on the stability of institutions and on the process of science. Dr. Hansen asked whether we could consider models of some sort to insulate the conflicts between universities and industry in these areas. Dr. Orbach responded that, indeed, a number of protections are provided in universities. Dr. Temin commented that perhaps this might be the case with universities in the Sun Belt, but the universities in the Snow Belt and Wisconsin are in trouble and are desperately looking for sources of funding.

Dr. Temin asked Dr. Sokol what he meant by goal-oriented basic research. Dr. Sokol responded that what he was really talking about here was more a matter of setting priorities, as in the corporation, and the need for industry to have input into the program development of NIH and the universities. It is really a question of balance, and in his view we need more of a leaning toward goal-oriented research. That, he said, is his perception, which is that of industry, and he realizes others may have different views.

Dr. Bondurant, in response to Dr. Sokol, remarked that it is important to realize that NIH supports not only pharmaceutical research, but also health research that cuts across many industries. Therefore, it would be difficult to set goal criteria for all the industries that might be involved. Dr. Sokol replied that he is speaking about areas related to drug research. At least in this area he would like industrial input on goals subtended by NIH and the universities.

Dr. Bondurant also responded to Dr. McDermott, noting that the medical schools are under severe stress and that the coming budget cuts in Federal support for medical education and the capping of Medicaid will have a profound effect on the research environment at the schools. He also asked Mr. Towbin how many cases there are per year where a health R&D firm, like Cetus, could receive $100 to $200 million in venture capital. Mr. Towbin replied that there are very few.

Department of Justice Antitrust Guide Concerning Research Joint Ventures

Joel Davidow
Director
Office of Policy Planning and Antitrust Division
U.S. Department of Justice

Mr. Davidow said that his prepared remarks and excerpts from the antitrust guide had been provided to the Committee. (See Attachment J.)

He said he would like to comment briefly on the antitrust law generally. He remarked that the purposes of antitrust laws are to ensure fairness to new businesses, to encourage free trade, and to prevent private division of the United States into separate markets. In effect, the division of markets and the choice of monopoly, if you will, are the prerogative of government in order to ensure free commerce and development. There can only be one government and no industrial efforts at self-government. Mr. Davidow added that much of the discussion today was on patents and the 17-year exclusion of others from their use. If a patent is obtained fraudulently, one can sue under antitrust as well as under patent law provisions.

Mr. Davidow cited examples of antitrust suits involving the American Medical Association and clinical pathologists. His examples illustrated two kinds of antitrust offenses. One is a per se violation--for example, price-fixing or boycotting. And then there is the rule-of-reason test, stated by the Supreme Court in 1911. It is a question of whether there is an unreasonable restraint of trade in particular circumstances, and here you get into a question of joint research ventures, as the antitrust guide describes. Under the rule-of-reason test, one must try to make distinctions between naked restraints of trade and restraint ancillary to a legitimate purpose. Thus, if you work at a joint research venture, you must ask whether a restriction ancillary to a legitimate purpose is reasonable. Examples from the antitrust guide cited in the material given to the Committee include the Salk Institute's request for a five-year exclusive agreement. The Justice Department, after successive reviews, stated that the purposes were legitimate: it was necessary to have the exclusivity in order to bear the risk for the research and development required. Another element of the test of reasonableness is whether the restraint is reasonable in scope and duration. The question of scope focuses on the field of use versus market divisions. Duration, of course, must take into account that the patent life is 17 years.

Mr. Davidow then described certain other joint research ventures and particular problems that arose. One was a suit in the 1960s against the American Automobile Manufacturers Association regarding a plan to have the member companies join in a research venture on auto emissions. There were certain charter restrictions, however, that in effect precluded changes without the unanimous consent of all those involved. Since there might be slower members who would retard the faster, more innovative members who wanted to introduce auto emission controls, there was concern on the part of EPA about inhibiting research or the utilization of its results. Mr. Davidow noted that clearances are generally granted for the joint research ventures that come to the Antitrust Division of the Justice Department for business review. For example, sixteen of eighteen requests were granted recently.

Dr. Temin asked whether one hears that our antitrust laws retard productivity and efficiency. Could Mr. Davidow comment on that in light of the Japanese experience? Mr. Davidow responded that Japanese industry is not dependent on monopolistic practices. Japan has eight automobile companies, all very competitive. He added that in Japan, as a matter of fact, several companies got together for joint research ventures on computers in order to catch up with our basic research and technology. Now that they feel they have done so, the joint ventures are broken off, and the companies can enter the market and compete successfully.

Second Day: Morning Session

IV. FEDERAL AND INDUSTRY SUPPORT IN HEALTH RESEARCH: COOPERATIVE RESEARCH RELATIONSHIPS

Introduction

Dr. Fredrickson opened the second day of the meeting by announcing the creation of the DAC task force on cost-sharing policies to follow up on the Committee's examination during 1980 of health research costs, including indirect costs. He also noted that the Committee had examined the concerns of universities regarding (1) Federal support in the face of steadily increasing costs of research institutions, (2) continuing differences in standards for indirect cost charges, (3) institutional needs for more flexible funding arrangements, (4) the impact of regular charter requirements on the cost of doing research, and (5) Federal auditing procedures, especially for time-and-effort reporting. Dr. Fredrickson noted that extensive proceedings of two meetings of the Committee had been included as a supplement to the NIH Research Plan, published in December 1980. On the basis of that record, the task force is being created to examine these reviews and develop recommendations for needed changes, including revised cost-sharing principles. The chairman of the task force will be Dr. Samuel Thier, and Dr. William Raub will serve as cochairman. DAC members will include Drs. Ivan Bennett, Louis Sullivan, Howard Temin, and Barbara Hansen. Task force consultants will include Mr. James Kelly, Dr. Linda Wilson, and Mr. Henry Kirschenmann, all of whom participated in the previous meetings of the Committee. The task force would begin work that afternoon, Dr. Fredrickson said, and he hoped they would develop an interim report for the June meeting of the DAC.

Dr. Fredrickson asked Mr. Staats to provide further information on whether Government agencies have used the march-in rights under patent agreements. Mr. Staats stated that he had called the relevant officials at GAO, who had conducted a quick survey, but could not document any instance of a march-in actually being implemented and resulting in the rescinding of patent rights. Indeed, he commented that in previous Commission reviews in the '60s and '70s, there was no instance found of the use of march-in rights, and the question becomes that of Dr. Siekevitz--whether, in fact, this is a real provision to be used. Mr. Staats added that under Public Law 96-517, the Patent and Trademark Law Amendments, there are stringent criteria set for march-in rights, but in his view, concern over the use of this provision is not warranted.

Corporate Support for Basic Research in Universities--New Directions

Dr. Cornelius J. Pings
Vice Provost and Dean of Graduate Studies
California Institute of Technology

Dr. Pings said that he had provided the Committee an outline of his remarks (Attachment K) and that basic information about the Commission is included in its report (Attachment L). As indicated in the report, the Commission was founded in 1978 by the American Council on Education, American Council of Learned Societies, Association of American Universities, National Academy of Sciences, National Association of State Universities and Land Grant Colleges, and Social Science Research Council. Funding was obtained from a variety of public and private sources. Eight of the 13 members of the Commission were from universities, two were from industry, and three were public representatives. The Commission issued five reports and concluded its work in June 1980.

In his remarks Dr. Pings reviewed possible modes of interaction between universities and industry, described past and present relationships, and explained why changes are needed for the future. Others, he said, had noted that basic research in universities requires long-term investment--certainly more than 10 years, which is often just the startup--as opposed to research employing venture capital, where, as Mr. Towbin noted, the basic research has usually been completed before the risk is taken. Dr. Pings urged industry to invest more in basic research, in their own facilities as well as in universities. He went on to review degrees of industry involvement in university research and appropriate roles for the Federal Government, industry, and universities. In sum, his institution, the California Institute of Technology, has had excellent relationships with industry. Indeed, it has a computer science program supported by eight companies, all fierce competitors. Each has one scientist who rotates through the program, and it has worked out extremely well.

Committee Discussion

Dr. Fredrickson asked whether there was any information on industry/government/university relationships in Europe, especially on the appropriate respective roles of industry in applied research and government/university in basic research. Dr. Pings said he was not aware of any information that might be available. Dr. Fredrickson complimented Dr. Pings on his superb analysis of the issues, and said that his questions set the framework for further exploration by the Committee. His presentation summarized many of the issues discussed the first day of the meeting.

Mrs. Jacqueline G. Wexler
President
Academic Consulting Associates

Mrs. Wexler also commended Dr. Pings for his excellent analysis. She feels that there is a mutual need here to develop better relationships. She believes that from her perspective as a university president, first at Webster College in St. Louis and then at Hunter College in New York, industrial support is clearly most important. At Webster College she came to know Dr. Throdahl (one of the participants at the meeting). His company, Monsanto, not only provided support for the college but was helpful in attracting excellent faculty members to teach physics.

She also commented on Dr. Philip Morrison's trip to Webster College to attend a seminar for junior high school teachers in program evolution. Its theme was to distinguish between directed task forces and free play, which are both necessary. She said that in looking at industry and universities, one might consider the same distinctions--namely, industry with applied research as "directed" effort and universities with basic research as "free play." But, she added, there has to be an overlap between both university and industry and basic and applied research. If each of these pairs were two circles, they would have to overlap, with a complementary area between them. She pointed out, for example, that industry is taking an increased interest in the support of training--as of engineers, because of industry's particular need for them.

She concluded with the comment that a good deal more discussion must occur at the scientist and administrative levels because there is still a great deal of distrust. The process, however, must proceed from the bottom up: scientist-to-scientist exchange is the key. You need good administrators to leaven the process and ensure scientific interaction. And the attempt to build better relationships is certainly worth the investment of time and effort.

Dr. David A. Wilson
Executive Assistant to the President
University of California (Berkeley)

Dr. Wilson provided a perspective from the University of California system. (See Attachment M.) This university has been cooperating with industry for years, especially the agricultural industry. The university's agricultural research and extension services have been extensively involved with agricultural business to improve research in that field. He also noted that in the health sciences there is much interaction with the drug industry. He commented that there has always been attention to industry/university relationships, but it became less visible because of the preoccupation with growth problems and the enormous increase in Federal support to universities. With tighter Federal budgets and dwindling student enrollment, attention can now return to a number of ongoing issues such as industry/university collaboration.

Dr. Wilson noted that a number of problems arise in this interface. For example, the University of California is suing a drug company regarding the ownership of a cell line, stating that the university rather than the company owns it. On the other hand, the university is being sued by a public interest group about its relationships with the agricultural industry and the assertion that the university is inappropriately using funds for the benefit of agribusiness.

One must recognize, Dr. Wilson emphasized, that the United States has an incredibly effective research establishment, built largely through Federal support of university-based research. There are points to be noted here--that only 3 percent of the University of California's research budget comes from industry, and this represents less than 1 percent of the total university budget. Therefore, industry support cannot substitute for present Federal support--and that is critically important to recognize in these discussions and the policy decisions that may be coming up. Further, industry participation in university research will not in itself increase national productivity. Lack of productivity is not due mainly to deficiencies in the union between industry and the university, but more to lack of investment capital, the tax structure, and the like. The opportunity in the collaboration is intellectual enrichment of the research process for both industry and the university and for the Government as well.

The ethos of the university tends toward pure research, and there is much negativism to targeted research sponsored by industry. Industry, however, knows the state of the art and the high-payoff research opportunities. The university research community can probably learn a great deal by working with industry. And government can serve as a facilitator, encouraging interaction. The research program administrator can provide gentle persuasion to assist this interactive process, and industry can encourage its scientists to work with university laboratories. An enlightened administration, as Mrs. Wexler noted, is very important in stimulating the scientific exchange.

Finally, Dr. Wilson observed, one should recognize that each partner can do certain things best. Industry makes the products; the university creates the environment for science, research, and the training of scientists; and government, through taxes and distribution, provides for a fair investment. Industry cannot be expected to support some kinds of research, because of a free-rider problem where others benefit without cost. That is the role of government, and thus Federal support for basic research is essential.

Dr. Frederick N. Andrews
Vice President
Purdue Research Foundation

Dr. Andrews reviewed issues at Purdue from his perspective as a research scientist and research administrator with 20 years in each role. For 25 of those years he has been heavily involved in university/industry relationships. He found Dr. Pings' analysis excellent and a superb framework for considering possible future relationships with industry. Dr. Andrews recited a number of reasons why relationships in the past have not always been good. Before World War II, he said, many of the schools at his university, including agriculture, engineering, chemistry, and pharmacy, were heavily involved with industry and very industry-oriented to get products into the marketplace. After the war there was a new generation of scientists and new faculty members, and they were primarily part of the enormous Federal investment in basic research. They lean toward the National Science Foundation and NIH for support. Thus, there is little interest in research on industrial problems.

This is compounded by the fact that industry makes few grants available, and those usually in small amounts. Most industrial contributions support Ph.D. theses and an occasional endowed chair and the like. Moreover, it is not realistic to expect large industrial investments in grants for basic research, especially with a prominent Federal role here of 30 years' standing. Most grants from industry range in the neighborhood of $250,000 to $500,000, occasionally reaching $1 million, and most of the investment is in sponsored research.

Dr. Andrews pointed out other problems related to publication and patent rights that bedevil university/industry relationships. Universities make knowledge available rapidly because that is how professors get their tenure. An assistant professor must publish, and as early as possible.

Most do not realize that one can apply for patents and that the delay in publishing is not that great. A myriad of corporations believe that universities cannot produce patentable items and that patent rights can vest only in corporations. That is nonsense, he said. He has found that the drug and chemical industry with which he has dealt does not have those views. But some corporations insist that all patent rights are theirs, and they often feel that providing support for students gives them the right to patent anything the student may be working on. On the other hand, the university provides services and training for the student and feels that, in return, the student's working efforts should be part of the university's holding. Some professors save their best ideas so as to market themselves as consultants to industry, and thereby deny universities the profit from these inventions.

Dr. Andrews, in concluding, said that Purdue has had excellent relationships with industry. Its formula is to put all the facts on the table so that industry has a clear idea of what the university intends, what its views are, and what is required for support. Most important is that in cooperative research relationships, ideas and concepts must be shared. There must be a mutuality of interest or there is no point in pursuing the relationship. As a final note, Dr. Andrews said that they had exercised march-in rights in several cases where they felt the public interest was not served by the licensing agreement or arrangements.

Dr. Philip Siekevitz
Professor of Cell Biology
Rockefeller University

Dr. Siekevitz reviewed potential problems and conflicts in this growing interest in the university/industry relationships. He made the distinction between private organizations (industry and institutions) versus public institutions that are accountable to the taxpayer. Universities constitute a substantial social investment; they are inherited resources that belong to us all. In industry, the major investment is for profit, with social needs important but secondary to that goal.

Dr. Siekevitz went on to say that in these difficult economic times priorities in the universities are shifting from social goals to returns on investment. He was concerned about the emphasis on patents, and asked whether proprietary rights will somehow damage or destroy the openness of the scientific process, with its peer review and open debate. He stressed, as did Dr. Temin, that dual allegiance, with possible conflict of interest, may develop when a professor attempts to do research and teach and also be a businessman trying to reap profits from his or her research.

And he noted that we must examine the impact of corporate support, especially from large corporations. He recalled that Mr. Towbin had pointed out during the first day that much of the investment in DNA came from oil companies and other major firms. He concluded by noting that universities, both public and private, are dedicated in large part to scientific research supported by the taxpayers, and careful attention must be paid to changing the present arrangements, with an emphasis on basic research, and social goals, to industrial research in which is implied the need for profit. (See Attachment N.)

Industry and Universities: Developing Cooperative Research Relationships in the National Interest--Report of the National Commission on Research

Dr. Raymond L. Orbach
Professor of Physics
University of California at Los Angeles

Dr. Orbach opened, noting that the Committee had an outline for his remarks and those of Mr. Throdahl, as well as a copy of the National Commission on Research report. (See Attachment L.) Dr. Orbach commented that there is no difference between public and private universities in regard to industrial involvement. However, the university looks at social needs; industry, at profit. The university/industry relationship is not a one-way street of ideas from the university that might lead to products for the market. There has to be a two-way exchange of ideas between the universities and industry. Dr. Orbach noted that Dr. Lepow had mentioned that 10 to 12 percent of all ethical drug profits are plowed back into R&D. That is a high figure, because the national average for all industries is 2 percent and clearly should be higher. Commenting on Dr. Andrews' perspective on patent problems in the university, Dr. Orbach said it is not as difficult as perceived for the university investigator to delay publication in order that one might file a patent application, and publication will be delayed for only a short time.

He went on to comment on Dr. Fredrickson's article in the New England Journal of Medicine, which was circulated to the committee members prior to the meeting. He noted Dr. Fredrickson's call for clinical experimentation and clinical trials, for which more public support will be needed. Similarly, he said, there is need for research on which regulatory decisions have to be made by the Federal Government, especially in the health and safety area. The National Commission looked at this sensitive subject, and there was agreement, as expressed in the report, that it might be useful if there could be a Government/industry/university partnership so that the university research community, with its widespread credibility, could set the science framework for regulatory needs, so that better and more reasonable regulatory decisions could be made on a firmer scientific base. He noted that regulatory agencies, such as EPA, have been shifting from procedural requirements to performance standards on science, and a good science base here would be especially helpful.

Dr. Orbach said that there are a number of ways to stimulate industrial investment in research at universities. One suggested approach to the Congress is tax credits for industrial investment in basic research in universities. Such approaches should be carefully explored. But the best reason for industrial support is the salutary effect of a heightened intellectual climate on the industrial environment. A climate for excellent R&D that can lead to better products for the marketplace, thereby increasing profits and enhancing industrial support of university science, would also provide fertile ground for recruitment of graduate students who will invest their futures in research in industry.

Monte C. Throdahl
Senior Vice President
Monsanto Company

Mr. Throdahl spoke about corporate investment, particularly among high technology corporations. He began by focusing on four rules regarding industrial investment in long-range research and development programs. They involve (1) time, (2) timing, (3) selectivity, and (4) uncertainty.

Regarding time, he reiterated the ever-present conflict between the need for immediate profits to support corporate research and development and the need for management patience in realizing the long-term payoff for many scientific achievements. Some examples: it took more than 20 years for the xerography technology to come to fruition; Monsanto invested 15 years in research and development for herbicides before really turning the corner; and there is a seven-year investment in plant cell biology that may take considerably longer for any commercial results to be achieved and brought to the public good. Further, when a process is developed, efforts are often made to develop more efficient substitute processes for a variety of reasons. In one such instance, it took eight years to develop a new process based on a different raw material to substitute for an existing one. Time is always an element for consideration by corporate managers and their boards.

Second, timing is also important in the development and use of inventions. He cited the earlier discussion on the "late bloomer" and the possibility that the technology may be too early or too late. If an invention is ahead of its time, that failure is very expensive; too late may also be expensive but better than not at all.

Third, initial selectivity is important. Generally, the first discovery is never the best one, and a better one usually follows it.

And finally, on the issue of uncertainty, one should know that this is not synonymous with risk. Uncertainty yields to risks when probabilities can be established, and then one spends dollars at an enormous rate.

Mr. Throdahl went on to examine the roles of universities. He noted that universities have a high degree of credibility in our society and should assist in the key scientific issues involving regulation. To date they have not contributed the data necessary for good regulatory decisions, as described by Dr. Orbach. So we need better rules for the university/industry "lash-up," a term coined by Mr. Throdahl and used in the National Commission report. He went on to describe the lash-up between Monsanto and Harvard, whereby Monsanto provides fundamental support for investigators at Harvard Medical School in areas of mutual interest.

As an introduction, Mr. Throdahl said that these kinds of agreements are difficult in the present climate, for companies have been required since the early '60s to issue quarterly statements of earnings, which have produced substantial pressures for profit performance. These statements are now like quarterly report cards for corporate managers, who have substantial impact on the use of corporate resources, especially those to be committed where a profit gain may be far in the future.

Given these constraints, Mr. Throdahl and Monsanto realized there were no easy ways to grow into new fields and sought with Harvard some area of mutual need and support to be explored with certain researchers at the medical school. They sought points of intersection in which each could serve the other. From this, after two years of negotiation, came an agreement for Monsanto to fund research teams at Harvard Medical School for 12 years. An evaluation midway in the program has shown that this is a social experiment that seems to be working quite well. They would not change the terms of the agreement except for fine tuning.

What brought them together, said Mr. Throdahl, was Harvard's interest in development of organs in relation to health and therapy and Monsanto's desire to support such research. Monsanto has been able to provide scaled-up chemical engineering, analytic techniques, organic synthesis, and a computerized library of rare chemicals, all of which have been of use to the researchers at Harvard. There has been superb collaboration. Decisions on planning and budgets are made jointly. Monsanto's Board of Directors has been fully informed about this program and has approved the arrangement and the funding. It was expected that there would be a $25 million commitment over the 12-year period.

Committee Discussion

Dr. Ivan L. Bennett, Jr.
Acting President
New York University

Dr. Bennett opened by reaffirming Dr. Wilson's comments that industrial support cannot substitute for Federal support of health research at the universities. However, there is need for additional cooperative research relationships. There can be scientific enhancement of all communities: the Federal scientists, the university scientists, and the industrial scientists. The university should provide Ph.D. candidates with a broader education, and with opportunity to learn industrial research. More exchange would benefit industry by keeping their researchers at the cutting edge of academic science.

Dr. Bennett emphasized Dr. Andrews' point that university scientists have a good deal to learn about industrial research. This generation of scientists has been primarily devoted to basic research, with support from the Federal agencies. It will take a good deal of work on all sides to educate university scientists about industrial research and the industrial scientist. For example, university researchers may think that with industrial support they can do the same kind of research under the same kind of conditions as with NIH funding. That cannot be the case, considering the constraints and requirements associated with industrial support, particularly nondisclosure of patentable or proprietary information.

Dr. Bennett went on to describe the difficulty of trying to get industry and university scientists at the bench level to exchange experiences and information. He cited an instance of a large corporation that had supported research in universities with only one condition--that their scientists freely interact. Promoting marriages between these groups has been extremely difficult. It will take time to deal with all the obstacles, but this meeting is a good device for calling attention to the problems.

Dr. Bennett brought up the issue giving industry tax credits for providing support to universities, which he believes has considerable merit. He cited the Canadian approach where industry is given $1.50 in tax credits for each $1 it gives to fund basic research at the university level. Dr. Bennett added that except for the drug industry, the agricultural industry is perhaps the best organized in its relationships with the academic sector and in bringing the results of biological research to the marketplace.

Concerning the marketing of useful products, it is important to distinguish the present interest in recombinant DNA firms from other health research. It is very rare to have investment capital provided for firms that have yet to make useful products. Generally, that investment is made only when there is clearly a useful product for marketing, and it is important to distinguish that here, as other speakers have.

Dr. Bennett concluded by noting that this is a most useful meeting of the Committee because it provides a means to examine industry/university relationships, whose adversary nature has too often been exaggerated. Indeed, cooperative research between industry and universities is most important. The goals may be different, but stimulation of the research process can be helpful to both.

Dr. Jack T. Sanderson
Assistant Director for
Engineering and Applied Science
National Science Foundation

Dr. Sanderson, of the NSF, provided perspectives on his agency's programs. He reiterated that this generation of university scientists has turned primarily to the Federal Government and never to industry for support. Twenty-five years ago, about 12 percent of all university research was industry sponsored. The proportion is now 3 percent, as Dr. Fredrickson pointed out. It is not that industry support has declined in absolute amounts, but that the Federal investment has grown.

Dr. Sanderson noted that the environment of the '50s and '60s favored the physical sciences as the '80s do the biological sciences. The enormous influx of venture capital tapered off in the late '60s. Thus the pendulum has swung back toward greater interest in support by industry, in collaboration with Government and universities. In Dr. Sanderson's view, there cannot be a return to the glorious '50s, except perhaps for certain fields in biology. In the '50s there were more dollars for research than perhaps could be used even today. Once again, however, there is a need, particularly in the areas of engineering and computer sciences. There are approximately 1,700 unfilled academic positions for engineers.

Dr. Sanderson commented on the bills that were considered in the last Congress. If the Vanik Bill had passed, industrial investment in academic science would have doubled. (See Attachment O.)

Dr. Sanderson went on to describe the NSF role. He gave examples of NSF's stimulation of collaboration, with sensitivity to the needs of all the parties. For example, NSF gave the University of Delaware funds for catalysis research. Through this effort the university has become a world leader and has developed a "critical mass" of research capability with national visibility, attracting significant industrial support as well. Another example, which has not met with success, is the Cooperative Automotive Research Program (CARP). Here nine areas were laid out with a good research agenda that was to have been initiated in FY 1980. However, with the economic straits of the automobile industry and the new agendas for Federal research, these efforts have been deferred and may not be supported in the near future.

Another, more successful, example is the NSF stimulation of university/industry collaborative research support. The point here was to get more communication going between industry and universities, particularly among individual scientists and engineers. The only constraint of the NSF support was that there must be a joint effort--namely, that industry must also actively participate in the research project. Simply providing funds is not enough. This has been particularly successful in such areas as engineering, where 46 percent of the dollars have gone. Other areas include chemistry and physics. Under this program university investigators have gained access to equipment and a chance for their ideas to move into useful marketable products. There is increasing demand for support here, and NSF will have to set stricter criteria in the face of limited funds for these projects.

Dr. Sanderson noted that there were other models of university/industry cooperation, such as generic technology centers. Here the thrust was that ultimately these centers would be independently funded by industry. Some have failed and some have been successful. Other projects have been direct support for innovation centers in the small business area, but they will now have to be phased out. Some are being picked up by industry or state government. Dr. Sanderson concluded by noting the basic complementarity of the roles here: Government support of basic research and industry support of applied research. NSF believes there have to be more experiments in developing collaboration, with or without direct Government participation.

Dr. Kenneth A. Smith
Associate Provost
Massachusetts Institute of Technology

Dr. Smith reviewed efforts in this area at MIT. He noted that several groups have attempted to get industry and university together. As Dr. Sanderson pointed out, very few have produced concrete results. One may ask why, with such good intentions, the attempts were unsuccessful.

Our system has been different from those in other countries. For example, in Japan and Germany there has been a much closer union between industry and universities, and in those countries industrial researchers frequently hold very high academic posts, bringing a great deal of prestige to both parties. Here, there has been perhaps a misplaced pride in "purity" at the university level.

There have been a number of problems, particularly in the area of patents and proprietary information. The new law will help, especially with the universities vis-à-vis the Federal Government, since agencies had differed so widely in their interpretations of patent policy. In the area of proprietary information, problems of concern to universities include requirements by the National Security Agency regarding cryptography and Department of Commerce (E.A.R.) and Department of State (I.T.A.R.) regulations on exchange of U.S. scientific and technical information with foreign countries.

MIT has policies regarding faculty who wish to direct corporate research. Currently, they may take two years' leave of absence, but when they return they cannot have any line responsibility in the corporation where they worked, to prevent conflict of interest. Dr. Smith noted that MIT has tried the experiment that Harvard declined to do--namely, forming corporations with direct MIT participation. MIT tried this 10 years ago, but the experiment proved unsatisfactory. MIT set up four such companies to facilitate the acquisition of venture capital, but the separation was never very clean. It was unclear whether the research ideas belonged to the university or the companies. MIT was associated with the companies and not very comfortably. Two of the companies have since closed and two are still functioning under a more distant relationship with MIT.

Dr. Smith briefly reviewed the Exxon agreement, which added $8 million over a period of 10 years to the MIT research budget, which is approximately $170 million each year. There has been no particular problem with Exxon regarding patent rights or the issue of licensing. Proprietary information can present a problem, though, particularly for graduate students, where the mandate basically for the university is free exchange of information, which is particularly important for students. It was resolved at the level of the presidents of MIT and of Exxon Research and Engineering. The arrangement is such that proprietary information is available to faculty and may be made available to students, but is not a condition of student participation in the project. Other problems crop up under different agreements, even with the same company, because the context can be quite different. For example, one faculty member obtained $40,000 support from Exxon, but it was necessary to write an entirely different agreement.

Dr. Smith went on to point out that there has been an evolution in cooperative research relationships between industry and universities. In the main they have worked quite well. Indeed, there have been no problems at MIT regarding emphasis on applied research within these agreements. Problems have arisen when faculty members seem to believe that they must focus on applied research and come up with products, but that has never been a condition. The evolution will continue slowly. Efforts in Congress such as the Vanik Bill or the new bills introduced by Representative Shannon and Senator Bradley are useful legislative mechanisms to provide for more industry research. The work will be hard, but in the end it will be worthwhile.

Dr. Walsh McDermott reflected that in his area of biomedical research the golden age between industry and universities was the period of the development of antibiotics. Clearly, one must accept the premise that the role of the Government here is primarily to provide support of basic research. One must consider that there are many barriers between industry and universities, but there are also barriers between the various scientific disciplines, such as physics, chemistry, and biomedicine. And medicine in particular provides special problems, in that much of the research is done with patients. NIH must determine its role in furthering industrial and university cooperation, especially among the investigators. Dr. McDermott said he had read recently that of 100 patients receiving antihypertensive medication, 83 who do not need it must be treated to cover the 17 who do. Identifying those 17 patients is a problem that should command the attention of both industry and universities. These are the kinds of problems that could be better addressed, and NIH needs to determine how it can serve as a facilitator. Dr. Temin added that perhaps NIH should consider some sort of industrial research associateship to assist university scientists to spend some time in industrial laboratory settings.

NIH Options and Policies

Dr. Charles U. Lowe
Associate Director for Medical
  Applications of Research (Acting)
National Institutes of Health

Dr. Lowe characterized this meeting as a watershed in terms of attitudes, procedures, and governance of NIH. (See Attachment P.) And as the meeting had brought out, a number of issues have led to the growing interest in industrial support for health research. These include (1) the passage of patent and technology bills, (2) the new NIH policy that would permit industry to receive short-term grants, (3) a new Administration position on technology transfer and private-sector development, and (4) a new role for NIH, which is one of the greatest if not the greatest source of health technology in the world, although faced with constrained resources.

Dr. Lowe briefly summarized his observations based on meetings he has held recently with industrial and university representatives on NIH policy, particularly in the area of patents. First, industry has a great deal of concern about the march-in rights provision of the institutional patent agreement. We need to consider solutions here that may deal with these concerns. Second, the patent issues loom large in terms of the success of the relationships, and therefore one must consider strongly supporting the National Commission on Research recommendations regarding enhanced industrial/university relationships and the role of NIH there. Clearly, the NIH role must be to strengthen the industry/university interaction. NIH must consider policies that identify the responsibility of the university in seeking a patent. If the university does not seek it, NIH can do so. It is clear that we need a better structure for decision-making and options, because NIH has the largest portfolio--64 percent--of active patents in the Government. And patents lead to the issue of money, which creates tensions among researchers and their institutions.

Dr. Lowe then pointed out some of the problems arising from this area of patents, particularly problems posed for the NIH peer review system, which is the heart of NIH and its strength. These problems are as follows: (1) Confidentiality of a scientist's annual report to NIH may not be complete because of patent or proprietary rights issues; (2) Study sections may inadvertently or intentionally take into account a principal investigator's potential profits from the proposal or other work; (3) In the content of the grant proposal, the principal investigator may fail to provide information or full disclosure; (4) There may be undue pressure on the peer review system, especially at the university, to reward principal investigators for patentable ideas.

Thus, Dr. Lowe said, NIH will have to give a good deal more attention to patent problems and must find mechanisms to encourage free exchange of information from NIH to industries and industrially supported grantees. We must be aware of discontinuity that may develop in the system because scientists who do basic research do not necessarily communicate well with those who do applied research. Finally, he said, the peer review system must be protected at all costs.

Dr. Fredrickson, in closing, thanked the members and the other participants. He noted that we have built a public record on issues that NIH collectively has not examined in the past. We will do so now, following the excellent suggestions heard today. The meeting was adjourned at 12:30 p.m.

Respectfully submitted,

Joseph G Perpich

Joseph G. Perpich, M.D., J.D.
Executive Secretary

National Institutes of Health
Bethesda, Maryland 20205
May 22, 1981

ATTACHMENTS

A (1) Letter of February 12, 1981, from Donald S. Fredrickson to participants. (2) List of members, Advisory Committee to the Director, NIH. (3) List of participants, Meeting of March 17-18. (4) Federal Register notice of meeting.

B (1) Fredrickson, D.S., Biomedical Research in the 1980's, N.Engl.J.Med. 304: 509-517, February 26, 1981. (2) Selected charts: National Cost of Health R&D, 1980; National Support for Health R&D, 1980; Health R&D Funds as Used by Industry and Universities, and Source of Those Funds, 1980 (% and $); and Health R&D Funds as Used by Industry and Universities,and Source of Those Funds, 1960, 1969, 1980.

C Diamond, Commissioner of Patents and Trademarks v. Chakrabarty: Decision by the Supreme Court.

D (1) Statement of Elmer B. Staats, Comptroller General of the United States, Before the Committee on the Judiciary, United States Senate, on S.414--The University and Small Business Patent Procedures Act (Wednesday, May 16, 1979). (2) Public lecture by Mr. Staats at Round Table on Science and Public Affairs, Duke University Graduate School, Durham, North Carolina, November 28, 1979: Current National Issues Involving Science and Technology.

E (1) Chart on U.S. Government patents prepared by the National Institutes of Health, February 20, 1981. (2) Summary of current HHS and NIH patent policies, including the current HHS patent portfolio and list of holders of institutional patent agreements with the Department of Health and Human Services, by Darrel Grinstead. (3) Schloen, L. H., and R. C. Herdman, This Business of Science Funding, Clin.Bull. 10(4):135-137, 1980.

F Section-by-section analysis of (1) The Patent and Trademark Amendment Act of 1980 (P.L. 96-517) and (2) Stevenson-Wydler Technology Innovation Act (P.L. 96-480).

G Federally Funded Research as a Basis for the Commercial Development of Medically Useful Products: The Viral Hepatitis B Story, prepared by NIAID staff for presentation to the NIH Director's Advisory Committee.

H (1) Charts prepared by the National Cancer Institute: NCI FY 1980 Obligations by Thrust; NCI Involvement With Commercially Available Antitumor Drugs; Division of Cancer Treatment, FY 1980 Obligations by SATT; Division of Cancer Treatment, FY 1980 Preclinical Contracts; Division of Cancer Treatment, FY 1980 Clinical Contracts. (2) The National Cancer Institute's Drug Development Program and Its Interaction With Universities and Industry, by Saul A. Schepartz. (3) DeVita, V. T., V. T. Oliverio, F. M. Muggia, et al., The Drug Development and Clinical Trials Programs of the Division of Cancer Treatment, National Cancer Institute, Cancer Clin. Trials 2:195-216, 1979. (4) Section-by-section analysis of Orphan Drug Bill (H.R.1663).

I (1) Hi-Tech Biomedical Companies, Initial Public Offerings, by Years, 1975-81, draft chart prepared by NIH. (2) Remarks by Dr. Herman Sokol, Bristol-Myers Company, for the Meeting of the Advisory Committee to the Director, NIH, March 16-17, 1981. (3) Health R&D Funds as Used by Industry and Universities, and Source of Those Funds, 1960, 1969, 1980. (See Attachment B-2.)

J (1) Cooperative Research Relationships and the Department of Justice Antitrust Guide Concerning Joint Research Ventures, by Joel Davidow, Director, Office of Policy Planning, Antitrust Division, U.S. Department of Justice. (2) Joint Research Guidelines for Industry, excerpted from Science 211:36-37, January 2, 1981. (3) U.S. Department of Justice, Antitrust Guide Concerning Research Joint Ventures, November 1980 (selected excerpts).

K (1) Outline of Remarks by Cornelius J. Pings for the NIH Advisory Committee meeting of March 16-17, 1981. (2) Notes on Practices and Policies in Selected Federal Mission R&D Agencies Concerning University-Industry Research Relationships, by Carlos E. Kruytbosch and Diane B. Weisz, Office of Planning and Policy Analysis, National Science Foundation, June 1980.

L Remarks by Raymond Orbach and Monte C. Throdahl concerning the report from the National Commission on Research, Industry and University: Developing Cooperative Research Relationships in the National Interest, with the report included.

M Remarks to NIH Director's Advisory Committee Meeting, March 17, 1981, by David A. Wilson.

N Siekevitz, P., Of Patents and Prizes, Trends in Biomed. Sci. 5(9):6, 1980.

O (1) H.R.1663 (Weiss bill). (2) H.R.1937 (Kastenmeier bill). (3) H.R.2472 (Shannon bill). (4) S.692 (Bradley bill).

P Biomedical Discoveries Adopted by Industry for Purposes Other Than Health Services, developed for the Director, NIH, by the Office for Medical Applications of Research, Office of the Director, NIH, March 2, 1981.

MINUTES OF THE
43d MEETING OF THE ADVISORY COMMITTEE
TO THE DIRECTOR, NIH

June 8 and 9, 1981
National Institutes of Health

COSTS OF BIOMEDICAL RESEARCH
and
GOVERNMENT-INDUSTRY RESEARCH RELATIONSHIPS

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43rd Meeting of the
Advisory Committee to the Director, NIH
June 8 and 9, 1981

SUMMARY OF ISSUES

Prepared by Joseph G. Perpich, M.D., J.D.
Associate Director for Program Planning and Evaluation
National Institutes of Health

I. WORKING GROUP ON COSTS OF BIOMEDICAL RESEARCH

A. Introduction

Dr. Fredrickson reported that the Working Group emphasized the need to approach the issue of total costs of biomedical research, rather than just indirect costs. And there was strong agreement regarding the legitimacy of public support for biomedical research, particularly in the fundamental sciences. It is important, however, to continue to examine that commitment in order to determine how the Government can get the best possible research efficiently and with good accountability. Much of the discussion centered around possible approaches to handling indirect costs. The following is based on an outline prepared by Dr. Wilson that serves as an attachment to the minutes.

B. Possible Approaches to Handling Indirect Costs

1. Maintain the Status Quo: Recovery of Indirect Costs Within Present A-21 Limitations

There was virtually unanimous agreement that changes must be made, as the present needs of the Government and the universities are not being met by the status quo. Faculty are unhappy with allocations for indirect costs; university administrators feel burdened by regulatory requirements imposed by the Government (including those contained in OMB Circular A-21); and Government program managers and auditors are concerned about friction generated by the present system and about the need to maintain accountability.

2. Maintain the Status Quo, With Improved Understanding of Indirect Costs

- Nearly everyone agreed that all parties should be made aware of the elements of indirect cost. Which costs are treated as indirect, and how are rates calculated and applied? Dr. Hansen suggested that indirect costs be discussed a good deal more at the university level so that faculty could be more fully informed on the rates. Dr. Merritt noted that indirect costs have received less attention from study section review groups in recent years. At first, they were listed on research proposals; then were shown as rates; and finally they were moved from the budget sheet to the worksheet. Should NIH and the universities try to make study sections more aware of these costs? Dr. Porter felt that many faculty are now so overburdened that further involvement in indirect cost considerations would take away valuable time from the laboratory.

- Mr. Kirschenmann urged focusing on the various elements of indirect cost to see whether all the parties can agree on which elements ought to be reimbursed. This matter is further discussed in the section on circumscribing recovery of indirect costs.

3. Treat More Cost Elements as Direct Costs

- Mr. Kirschenmann felt that treating more cost elements as direct costs would increase study section confidence in assessing the total costs of a research project. Dr. Thier and others pointed out, however, that this would only result in a change in distribution, rather than in total cost.

- Dr. Wilson observed that this approach could have an adverse impact on allocation of dollars for use of shared facilities and would require extensive revision of current university budget practices. She noted that many universities support direct costs of research, as well as indirect costs.

- Dr. Brown urged this as a partial approach to the problem. He pointed out that study sections scrutinize direct costs rigorously in terms of whether they are required for the proposed research. Indirect costs are negotiated with Federal personnel, who only determine whether a given item satisfies the accepted definition of indirect costs. It is not feasible for them to determine whether a given item of indirect cost is needed as part of an efficient operation, or even whether it is needed at all. This problem would be alleviated by moving as many costs as possible from the indirect to the direct category.

4. Change the Mechanism for Reimbursement of Indirect Costs From Project-by-Project to an Aggregate Settlement

Dr. Ellis commented that the NSF experiment with the multiple grant award proved to be unsatisfactory for both the universities and the agency. The universities continue to monitor research on a project-by-project basis, for reasons cited in Dr. Wilson's paper.

5. Circumscribe Recovery of Indirect Costs

- There was a good deal of Committee discussion concerning this approach, especially on the potential for limited recovery of certain elements of cost. Dr. Fredrickson asked Mr. Kirschenmann to rate the various components of their justification from Congressional and Administration perspectives. Mr. Kirschenmann noted that there is little argument on reimbursement for operation and maintenance or for use allowances on equipment. To research administration and general administration, he assigned a second order of priority. He ranked libraries third and departmental administration fourth. The fourth category represents approximately one third of the indirect cost rate and seems to raise the most questions in the mind of Congress, the Executive Branch, and indeed the faculties.

- Dr. Brown recommended uniform indirect cost rates within each region having relatively uniform fuel costs, as explained in his article in Science. (See Attachment J.) These uniform rates would be adjusted upward only if there were compelling evidence from the universities that this was necessary. This type of policy seems essential to break the upward spiral of indirect cost rates, which is continuing at an alarming pace.

- Prospective increases in indirect cost rates might be held to some function of inflation and appropriation available. There was a good deal of Committee discussion on the extent to which indirect cost reimbursement covers the costs of research. Dr. Thier and others felt that there is currently an underrecovery, especially in the face of escalating energy and labor costs. Mr. Kirschenmann agreed. Dr. Ramey, however, asked why universities are encouraging principal investigators to seek grants if the grants are costing the universities more than they receive from the Federal Government as support. Mr. Staats pointed out the difficulty in limiting indirect cost rates, especially when costs vary so greatly in different parts of the country. It was also mentioned that the university, with regard to grants (as opposed to contracts), does not expect full recovery of costs.

6. Reduce Not Only the Reimbursement of Indirect Costs but Also the Costs Themselves

- Drs. Thier and Hansen stressed the need for greater efficiency at both the local and Federal levels. Dr. Wilson observed that cost-reduction systems developed by universities have probably reduced the rate of increase more than many people realize.

- Dr. Hansen urged that the Government assist the universities by reducing their regulatory burden. Mr. Staats added that in view of the climate favoring deregulation, it is appropriate to examine all regulatory requirements, including those in Circular A-21.

- Use of a fixed-obligation grant may reduce costs. There was strong support for a trial of this concept, which was developed by Dr. Wilson and Mr. Kelly. Under a fixed-obligation grant, the award would be made on a lump-sum basis, with the understanding that indirect costs would be charged in accordance with federally approved rates. Grants management would be delegated to the investigator and institution, except for changes in scope, principal investigator, or institution. Budget flexibility for direct costs would be limited only by established institutional policy and the principal investigator's determination of prudent scientific management of the funds.

- At the same time, the Federal Government would forego such regulatory requirements as time-and-effort reporting, with more emphasis on technical and scientific accomplishments.
- Dr. Brown emphasizes in his Science article that one advantage of regionally uniform indirect cost rates is that they would substantially reduce indirect costs. At present the considerable cost to universities of frequent renegotiations of indirect cost rates is charged to indirect costs. These frequent renegotiations are also expensive in terms of Federal personnel who participate in the process. Similarly, under the present system the universities incur substantial indirect costs in demonstrating accountability for indirect costs, and this issue is likewise expensive in terms of Federal personnel. Under regional uniform indirect cost rates, each university would receive indirect cost funds that were deemed equitable, and the actual uses of those funds would become irrelevant. Hence, the issue of accountability would be largely solved. This would render unnecessary many of the provisions of A-21, to which the universities have objected violently, and many of the current costs of assuring accountability would likewise disappear.

7. Increase Productivity

The Committee agreed that attention must be paid to increasing research productivity, perhaps through greater use of communal or shared resources.

II. WORKING GROUP ON COOPERATIVE RESEARCH RELATIONSHIPS WITH INDUSTRY

A. Introduction

The issues in this section were considered in the framework of the Patent and Trademark Act Amendments discussed at the DAC meeting in March and again in June. The Committee generally agreed that the law will not change NIH policy in a major way. In effect, the law provides a statutory basis for current policy. Of much more significance have been the striking increases in private capital invested at universities in the biomedical sciences, such as molecular biology. This change must be examined for its impact on the system. However, a number of issues related to the Act were highlighted at the DAC meeting, a few of which--as outlined by Mr. Grinstead--follow.

B. The Act requires that inventions be reported within a reasonable time and that grantees and contractors submit (1) invention reports when inventions are made, and (2) utilization reports to determine whether inventions are being implemented. Dr. Pings urged that a heavy reporting burden not be imposed under the implementation regulations.

He noted that the Federal Government has 30,000 patents, of which 1,600 are active, with licenses. Requiring annual reports on all patents, for example, could produce an enormous burden with very few practical results. Others shared Dr. Pings' view.

- There was considerable discussion at both the March and June meetings regarding the march-in authority under the Act. Mr. Hutt noted that standards and procedures for the invocation of this authority must be clearly specified. He said that industry needs (1) protection for invention rights and (2) certainty of policy. The march-in provision strikes at the heart of these two needs. Special attention will have to be paid to the criteria used here. Dr. Andrews and a number of Committee members supported the march-in provision, which they view as required to protect the public interest in specified cases.

- The Act is silent on the handling of disputes or appeals that may arise in its implementation. It requires universities and non-profit organizations to share royalty returns with inventors. There seemed to be general agreement that the Government should not interfere in royalty rate allocation at the university level.

- Dr. Merritt urged that the patent system and implementation regulations be discussed with faculty. In view of the increasing interest in private-sector financing, it is most important that universities inform newly recruited faculty members about the rights of investigators and universities (much as they now do about tenure and other rights and responsibilities).

- Mr. Hutt urged that NIH consider the possibility of creating Business Patent Agreements (BPAs) similar to the Institutional Patent Agreements (IPAs). He noted that the IPAs were created without a statutory base as, indeed, were many NIH innovations. In fact, one could go further without a statute.

- A number of questions were raised about the protection of proprietary information in study section reviews. Dr. Douglass of DRG noted that study sections are not currently involved in considering protection of proprietary information on patent rights. However, Dr. Gartland indicated that the Recombinant DNA Advisory Committee has developed procedures that have operated reasonably well in this sensitive area. Mr. Hutt commented that, with proper guidance, the study sections could also handle the problem.

- Dr. Merritt raised the issue of the Act's impact on NIH grants and contracts administration, and the needs (1) to arrange for administering federally funded inventions and patents at universities and other organizations, (2) to establish reporting requirements that fulfill the statutory obligations, and (3) to enhance the technical and administrative capabilities of Federal agencies in relevant areas pertaining to commercialization of R&D.

III. HYBRIDOMA: A CASE MODEL

A. Introduction

The science and applications of the hybridoma technique were described by Drs. Scharff and Krause. Dr. Meyer reviewed the Bureau of Biologics' role in approving applications for products derived from the technique. Related policy issues were discussed:

1. Invention Reporting, Patenting, and Development

The key issues are (1) What should be patented? (2) Who should patent it? and (3) What guidelines should NIH provide in this area? These matters prompted considerable discussion. Dr. Scharff pointed out that all hybridoma cell lines are potentially patentable, and in view of the fact that a single laboratory can produce 20 to 30 hybridomas per month and a shared laboratory up to 100, one can see the enormous problem in reporting these discoveries. Dr. Adams calculated that one could spend half of the Nation's gross national product just to patent hybridomas!

2. Distribution and Deposits of Cell Lines

- Dr. Cohn described the cell line repository at Salk Institute, pointing out the requirement that all patented cell lines be placed in an official repository, where they become available to others. Inventors must agree to permit lines to be loaned prior to placing them in the repository. Likewise, investigators must agree not to use the lines for other than scientific purposes without the approval of their inventors. Dr. Scharff believes that this is one beneficial aspect of patenting.

- Questions were raised, however, regarding situations where inventors may not wish to patent--for example, in order to retain the hybridoma as a trade secret, or to dedicate the invention to the public.

3. The Peer Review Process and Commercial Involvement of Investigators

- Here again the key issue is the commingling of funds and how to handle it at the university level. Questions were raised regarding the Massachusetts General Hospital agreement with Hoechst. Dr. Lamont-Havers explained that the existing MGH policies on patenting and consulting will govern here. Several questions were raised on their applications to investigators working in the molecular biology department funded by Hoechst, particularly in regard to consulting arrangements and patenting and licensing, and especially where there is commingling of funds.

- A number of questions emerged from Dr. Adams' presentation on the work of Hybritech. What should be the appropriate split between Federal and private-sector support for research in this area? (Much of the basic research was funded by NIH.) What should be the nature of support for clinical research? Can the private sector do most of it? What will be the role of industry in R&D on "orphan antibodies"?--equivalent to orphan drugs. How can a conflict of interest between the university laboratory and the industrial laboratory be handled, especially where there are exchanges of investigators and commingling of funds? And where there is commingling, what policies will govern the allocation of patent rights, licensing, and royalty rates? These questions will be addressed by the Working Group on Cooperative Relationships With Industry.

ADVISORY COMMITTEE TO THE DIRECTOR, NIH
Minutes of the 43rd Meeting, June 8-9, 1981

Prepared by
Joseph G. Perpich, M.D., J.D.
Executive Secretary

The 43rd meeting of the Advisory Committee to the Director, NIH (DAC), was held at the National Institutes of Health, Bethesda, Maryland. Dr. Donald S. Fredrickson chaired. (See Attachment A for list of members and participants and letter of invitation.)

First Day: Morning Session

Introduction

Dr. Fredrickson began by noting that this meeting represented the most recent stage in the evolution of the Committee's examination of the relation between government, university, and industry in the support of health research at universities. In a recent address to the American Federation for Clinical Research at San Francisco, he had spoken on the theme of community resources and community decisions--namely, how best to manage the resources of NIH and the scientific community in the face of severe fiscal constraints. The stabilization of research project grants--the strategy of NIH in which the DAC played an important part--must now be followed by stabilization of the research environment. Clearly, the Government, industry, and universities should examine this in concert. Dr. Fredrickson noted that two working groups have been created under the aegis of the DAC to examine the issues and make suggestions to the full Committee for consideration by NIH, the Department, and government generally. The morning session would be devoted to reports of the Working Group on the Costs of Biomedical Research, chaired by Dr. Samuel O. Thier and cochaired by Dr. William Raub. In the afternoon and the morning of the second day, the Committee would hear reports of the Working Group on Cooperative Research Relationships With Industry, chaired by Dr. Ivan Bennett and cochaired by Dr. Charles Lowe.

Dr. Fredrickson observed the continued interest in the area of Government-university relationships as evinced by the activities of the National Commission on Research, the work of the DAC, and the National Academy of Sciences' recent creation of a special committee to examine those relationships. (See Attachment B for NAS committee membership.) Dr. Fredrickson noted the increasing number of articles being written in this area, including the recent one in Science magazine by Dr. Gutowsky. (See Attachment C.) One of the major areas of concern is that of indirect costs and the application to those costs of accounting principles contained in OMB Circular A-21, as emphasized by Dr. Gutowsky in his article. Dr. Fredrickson then referred to an NIH budget breakdown that identifies the portion devoted to indirect costs. (See Attachment D.) Dr. Fredrickson said that the Government indeed recognizes indirect costs as real costs for which the universities must be reimbursed, but that some academic scientists, as mentioned in previous meetings of the Committee, eye suspiciously any progressive increase in indirect costs as representing a "steal" from the purse available to support their research. Nevertheless, the grants program recognizes that grants require cost-sharing.

Dr. Fredrickson said he looked forward to today's discussion, especially to the consideration of new initiatives to maintain the appropriate balance in shared costs. One such initiative is the "Fixed-Obligation Grant," which involves preaward negotiation of both direct and indirect costs in a single fixed sum. One advantage of such a grant would be a considerable reduction in time-and-effort reporting now required by the Government under OMB Circular A-21. With that introduction Dr. Fredrickson then turned to Dr. Thier for a report of the Working Group on the Costs of Biomedical Research.

I. PRESENTATION OF ISSUES BY THE WORKING GROUP ON COSTS OF BIOMEDICAL RESEARCH

Introduction and Overview: The Costs of Biomedical Research

Samuel O. Thier, M.D.
David Paige Smith Professor
of Medicine and Chairman
Department of Internal Medicine
Yale University Medical School

Dr. Thier briefly described the mandate and membership of the working group. (See Attachment E for mandate, membership, and minutes of the two working group meetings.) He emphasized the worldwide support of biomedical research. In the United States that support is not largesse, but is designed rather to foster national purpose. The Government, principally through NIH, aims at the best possible research, conducted in the most efficient manner, with good accountability. Dr. Thier went on to point out that NIH research support was approximately $700,000 in 1940; $60 million in 1950; $1.1 billion in 1970; and $3.4 billion in 1980. Indirect costs averaged 8 percent in 1955, 15 percent in the late 1950s, and approximately 20 percent in 1963. In 1966 the concept of cost sharing was introduced and new rules for reimbursement went into effect.

Dr. Thier observed that a major concern, particularly among investigators, has been the continuing rise in indirect costs during a period of fiscal constraints. Concern has been expressed about the rate of that rise, the variability of indirect cost rates among institutions, the perceived need for more research dollars for direct rather than indirect costs, the proposed limit on institutional support for indirect costs on training grants, and the prospect of a cap on indirect costs.

With these concerns as a background, Dr. Thier then identified four basic tasks for the working group to undertake. The first is to review the definitions, with the object of educating Federal officials and the broader scientific community on indirect cost elements. The second task is to examine implications and impacts on research institutions if indirect costs are capped, or limited. The third is to consider alternatives to reimbursement for indirect costs and to review research funding in general. Finally, on the basis of these examinations, the group will make recommendations to the Director's Advisory Committee at its next meeting in October.

Dr. Thier then expanded on the issues outlined above. He noted that one must first of all stress that indirect costs are real costs of doing research and that the universities, within the cost-sharing framework, are not at present recovering all of their allowable costs. This contrasts with industry, where all indirect costs are recoverable. Dr. Thier noted that there are two major areas that account for indirect cost rate increases at the universities: (1) facilities and utilities (primarily energy and labor costs), and (2) administrative costs, particularly in meeting the large number of Federal regulation requirements pertaining to such matters as protection of human subjects, occupational health, and the like. Here costs have increased more rapidly than total indirect costs or the general inflation rate.

Dr. Thier said that indirect cost rates vary. (Mr. Kirschenmann had earlier documented a range from 30 to 100 percent.) All rates are covered by rules for allowability that are subject to interpretation. Moreover, the rates vary because the denominator varies--i.e., indirect costs may be based on salaries and wages, on total direct costs, or on total costs. Indirect costs also vary regionally, with institutions in the Northeast incurring higher energy costs than those in the South. Another factor is the research mix at the universities, and this derives from the nature of the research. Thus, there can be no valid basis for comparing indirect cost rates among institutions. Equity depends upon having standard ground rules for the determination of costs.

Dr. Thier observed that the variation among university rates can be seen in a different light if one looks at the indirect cost rate as a percent of the total cost of research at the university. Mr. Kirschenmann did a quick review of NIH support at selected universities, calculating the amount of dollars for indirect costs over the total amount of dollars those universities received from NIH. The variability is in the range of 20 to 40 percent. State and public institutions are at the lower end, private institutions at the higher end. Basically, one cannot draw conclusions simply from the differences in indirect costs, especially when both the denominator for the calculations and the research mix at the universities are different.

Dr. Thier also pointed out that it does not make sense that industry can recover all its costs while universities cannot. He said he hoped that Mr. Staats in his presentation would provide better reasoning for the concepts of procurement versus assistance that underlie the differing treatment of industry under contracts and universities under grants. In Dr. Thier's view all Federal R&D funding is really in the nature of assistance that provides a mutual benefit to the Government on the one hand and the universities or industry on the other.

Dr. Thier said that the working group will also consider the whole question of direct versus indirect costs. He felt that funds could not be taken from indirect costs to support direct costs, because laboratories need heat and maintenance personnel, which indirect costs support. Further, if indirect costs are limited, then the universities will begin to shift indirect cost items into the direct cost categories. Thus, the costs of research will not change, but only the distribution. And if energy costs continue to rise and a limit is imposed on indirect costs, there will be a diminished capacity for research at universities. The Government must either underwrite its own laboratories or protect the present system of biomedical research at the universities. There are two choices: innovation and education in the face of retrenchment, or a limitation on indirect costs with a reduction in our Nation's research capacity.

Finally, we must seek alternatives to assure autonomy for the universities and investigators, and accountability to the Federal patrons.

Dr. Thier noted in conclusion that he had met with Dr. Burke Marshall, chairman of the NAS committee, and they had agreed to keep each other informed on the work of the two groups. In his view the NAS committee will be dealing more with generic long-term issues and the DAC working group with immediate questions. Dr. Fredrickson observed that we must be optimistic, that the NIH and the Department are receptive to ideas and suggestions, and that it is possible to change the way NIH does things. We can and must explore cooperatively changes in our procedures that will meet the needs of both the Government and the universities.

Federal Procurement and Assistance Concepts: Overview

Elmer B. Staats
Former Comptroller General of the United States

Mr. Staats reviewed briefly the history of the development of OMB Circular A-21. Initially, the Bureau of the Budget received many inquiries from Federal agencies concerning varying practices among granting agencies in respect to cost reimbursement. Thus, the first document in what became the OMB Circular A-21 series originated in requests from Federal agencies. It was simple and brief. Now, however, it is a highly detailed regulatory document which, recently revised, is linked to the process now under way to examine biomedical research costs and Federal accountability requirements.

Mr. Staats took note of the work of the National Commission on Research, the DAC, and the new NAS committee on which he serves as a member. He said that in the interests of uniformity, the revisions of Circular A-21 now require that all indirect cost rates be based on total direct costs rather than salaries and wages or the variety of other bases that universities have used

in the past. He observed that there does appear to be a perception, particularly among investigators and faculty, that the university administration is getting a "free ride" out of indirect costs. On the other hand, some have suggested that indirect costs are in part rising because universities are employing better and tighter auditing controls in the face of tight budgets, whereas in earlier years, with rising enrollments and burgeoning income, universities did not charge the full costs of doing research.

Another problem has been cost sharing. Mr. Staats reviewed the Congressional Appropriations activities here, particularly in 1975, when it was noted that the Government and universities share the same goals and should therefore share in the costs of doing research. This cost sharing issue is one that has bedeviled the Government-university relationship.

Mr. Staats said that indirect cost rates have been rising because of such things as energy and salary scales. He pointed out, as Dr. Thier had done, that there have been suggestions of applying a cap, or uniform rate, across the board. The uniform rate would have the advantage of minimizing invidious comparisons among institutions, and it would be easier to calculate. The GAO, however, in its study of indirect costs, had concluded that a uniform rate was not feasible. (See Attachment F.) Probably the major flaw in this approach is that costs differ for institutions. Maintenance and fuel costs vary across the country, depending on the region, the age of university buildings, and the kinds of research performed.

In its report GAO criticized the cost reimbursement principles under Circular A-21, and supported revision. It recommended that new approaches be taken, such as allowing for disclosure statements whereby universities would document their accounting systems and the methods used to develop indirect cost proposals. Such disclosures would be made for the initial proposal, and thence only for changes in the accounting system. (See page 37 of the GAO report.) The GAO separated the concept of cost sharing from the issue of indirect costs. If the Congress should desire to limit Federal reimbursement, this should be achieved through some formal ceiling on the basis of total costs, rather than just the indirect cost portion of research.

Mr. Staats also reviewed briefly the Federal Grant and Cooperative Agreement Act, noting that it reflects recommendations from the Cost Accounting Standards Board. This board provides the cost accounting standards for contracts. It permits, for example, reimbursement for interest as a cost of Government contracts. This is not the case for grants. In addition, independent R&D (IR&D) may be conducted under contracts. Such funds can go only to companies receiving contracts and are proportional to the total contract amount. (Roughly a billion dollars is provided for in this way).

Mr. Staats pointed out that the funding of IR&D is basically a grant. We need to examine this aspect for purposes of the grant programs. He suggested consideration of a number of changes, such as multiyear funding rather than the present stop-and-start approach, which is far more expensive to administer and costly for all parties involved. We should also be looking at the grant system and at unallowable costs. We should try to get the program and audit people on the Federal and university levels to work together more closely. Auditors could work with grantees on the approval of systems, much as they now do with respect to contracts.

There is a principle underlying contracts that Mr. Staats believes should apply to grants: All identifiable indirect costs should be included as part of the total costs for doing the research. Mr. Staats noted that the cost accounting standards provide that all allocable costs be met in commercial work done under contract. Different rules apply under the assistance concepts that govern universities. In the grant, responsibility for performance, according to the Procurement Commission, rests with the recipient, and there should be little or no Federal interference. The recommendations of the Procurement Commission served as the basis for the Grants and Cooperative Agreement Act, which attempts to define more clearly the difference between the contract on the one hand and the research grant on the other. The Procurement Commission has also suggested that the OMB provide guidance for changes in assistance programs. In March 1980 the OMB set up an entity within itself to recommend such changes to the Congress.

Mr. Staats also observed that in the present climate emphasizing deregulation it is most appropriate to reopen the issues concerning Circular A-21. OMB is now working out a deregulatory program under initiatives from the President, and clearly Circular A-21 could be included. Mr. Staats felt that something better was needed than the current time-and-effort reporting and the computing of indirect cost rates. Perhaps it would be useful to explore a single interface for auditing between the Government and the university. Obviously, it would be useful to have one point in Government for purposes of auditing. An alternative approach, such as the disclosure statements recommended in the GAO report, would go a long way toward fulfilling both Federal and university needs.

Finally, Mr. Staats noted that the NAS committee on which he serves would be a useful forum in which to discuss these broader issues, much as the DAC is serving as the Government forum.

Committee Discussion

Dr. Doris Merritt
Special Assistant to the Director
National Institutes of Health

Dr. Merritt briefly reviewed the history of the growth of universities. She noted that many university administrators have never been faculty members, but their salaries in many instances are rising faster than those of faculty. Naturally, this has generated concern and conflict. In view of the importance of faculty and scholarship in the university, it is essential that faculty be fully informed and participate in decisions that affect them.

Dr. Merritt went on to say that in her view indirect costs have, in effect, been "swept under the rug." In the past, indirect costs were put on the budget pages and all the study section members saw those figures. Now the others had, that grants are not paying the full costs of research and that universities are going more and more into the hole. Other sources, such as State budgets, are getting just as strained as the Federal budget.

Dr. Fredrickson noted that there is general agreement on the legitimacy of Government support for scientific inquiry and that the commitment is as great as it ever was. But there has always been a different attitude to Federal support for teaching.

He went on to the emerging theme that it was necessary to examine the total costs of research. Clearly, Government may not be able to bear the whole burden. Universities bear some of it and will continue to, but the question is, How much? We must consider this in the light of the need to lessen the burden on universities, and one consideration is to negotiate on the basis of total costs of research. He asked Mr. Staats whether universities would be in a position to handle the negotiation of total costs. Are their auditing systems up to the task? Mr. Staats replied that some universities are indeed up to the task, and that all are potentially capable of handling the task with experienced program and auditing people. Indeed, universities are becoming more and more like businesses in the sense of accounting for the costs of doing their work.

Dr. Fredrickson then asked Dr. Merritt whether in her view the NIH is up to negotiating total costs. Dr. Merritt replied that she thought so, but it depends on (1) the ability of Government auditors to see the universities' systems as sound and appropriate, and (2) the ability of study sections to handle both the science and the total budget.

Mr. Kirschenmann responded that these are tough questions and that there are two basic considerations here that need to be addressed. First is the confidence of the study section members in the fiscal judgments of the proposals submitted--i.e., whether the research resources requested are reasonable and fair. If the judgment is that they are, then the cost aspects flow easily. The second is the question of what NIH and the scientific community believe should be paid for administrative costs. Should grants pay for research administration? If there is agreement on this, they can be paid. But there is a good deal of disagreement in this area.

Indirect Costs: University Profiles

Mr. Henry G. Kirschenmann, Jr.
Deputy Assistant Secretary for Grants and Procurement
Department of Health and Human Services

Mr. Kirschenmann began by reviewing the material he had prepared for the working group. (See Attachment G.) Referring to a table on indirect cost rates at 39 colleges and universities, he noted that for those universities that calculate indirect costs as a percentage of salaries and wages, the average indirect cost rate is 66 percent; for those that calculate on the basis of total direct costs, the average is 47 percent. Of the indirect cost total, approximately 30 percent goes for administration--departmental and research--and approximately 36 percent goes for facility costs.

indirect costs are negotiated apart from the scrutiny of the investigators and faculty. Moreover, indirect costs have been cited as a percentage on the budget page. Now, with the new forms, they will not appear on the first page or budget page, but on the worksheet. It is essential that indirect costs be explained to the principal investigators. NIH has a responsibility here to educate investigators and university administrators alike on the total costs of research. A much better exchange of information is essential. Dr. Fredrickson commented that the theme emerging from these discussions was the need to focus more on the total costs of biomedical research, rather than on the direct or indirect cost components.

Dr. Fredrickson then opened the meeting to general discussion. Dr. Ramey asked Dr. Thier if he could explain his statement that indirect costs do not pay for all of the university costs for research. Dr. Thier suggested that perhaps Mr. Kirschenmann could answer that question better than he. Mr. Kirschenmann noted that there are a number of costs that are not allowed, such as the costs of interest. Others are the costs of public relations, fund raising, and independent research and development. As Mr. Staats had pointed out, IR&D costs are recognized for reimbursement to commercial organizations under contract. Mr. Kirschenmann added that the OMB is considering recognition of costs such as interest rates. He opposes reimbursement for IR&D costs to organizations (profit or nonprofit) whose primary purpose is research. In effect, there should not be funding for IR&D through the indirect cost rate.

Dr. Fredrickson asked whether universities are really going into the hole in support of research activities. Mr. Kirschenmann replied in the affirmative. Moreover, with pressures on tuition and other sources of funding, such as State revenues, it will become increasingly difficult for them to subsidize the costs of research. Dr. Ramey asked if it was true, then, that the more research there is at a university, the more in the hole it may go. Mr. Kirschenmann said this was so, especially if the university cannot recoup the costs through other sources, such as tuition and State funding. Dr. Ramey observed that universities still want principal investigators to get more grants. The implication is that this assists in university support. Mr. Staats, speaking as a university trustee, observed that a major factor in encouraging faculty to seek grants is the assumption that the policy attracts better faculty and graduate students. In addition, Mr. Kirschenmann noted that if faculty are engaged full-time in teaching, the university must pay all of their salary, but if faculty get grants, the university will only have to pay part of the salary.

Dr. McDermott asked whether universities are manipulating the items under direct cost in order to recover more indirect costs. Dr. Wilson pointed out that the universities support direct cost items too, such as computer time and the like. Furthermore, the universities frequently must provide the resources in those periods when projects are over and new projects are yet to begin. The universities do not get money for this, although the NIH does provide assistance in the termination of the grant or if a new grant is to come up in a short period of time. Dr. Wilson noted that basically faculties want to do research, and universities therefore encourage research. She pointed out, as

A second table provided by Mr. Kirschenmann showed indirect cost rates with component breakdown at the 39 institutions over a three-year period--1978, 1979, and 1980. No trends were discernible. If, for example, one examines the Yale figures, one sees that the indirect cost rate dropped from 76 to 55 percent because the base was changed from salary and wages to total direct costs. However, administrative costs changed very little--approximately 3 percent. At the University of Massachusetts, where indirect cost rates rose from 65 to 75 percent (applying the same base), there were no changes in administrative costs, and costs for facilities decreased from 18 to 17 percent. At the State University of New York (Downstate Medical Center), the indirect cost rate went from approximately 63 to 70 percent, though facility costs fell one percent. At Northwestern University, there was no change in the indirect cost rate, but there were changes in the rates for administration and facilities.

Mr. Kirschenmann noted that in developing an indirect cost rate an institution obviously considers other factors than those specified in Circular A-21. In Mr. Kirschenmann's view, the rates in many instances are probably lower than they should or could be. This reflects, on the one hand, the university wanting to keep the rates down because of faculty concerns, and on the other hand, trying to recover as many of the direct costs associated with the research as possible. Mr. Kirschenmann said it was unclear whether universities generally developed the indirect cost rate first and then calculated the total costs required for the research or whether they calculated the total and then arrived at an indirect cost rate--that is, whether the indirect cost exercise is designed to identify an institution's true overhead costs or whether it is a reflection of the amount an institution decides it must recover to fund its research programs.

He also noted the special concerns of the Federal Government, the Congress, and the faculty regarding administrative costs in indirect cost calculations. He referred to the checklists (see Attachment G) provided by various universities citing their administrative activities covered by indirect costs. These include executive committees, standing committees, councils of the general faculty, and several other college committees. Mr. Kirschenmann said he takes no position on these items, but it is essential that there be some consensus about the appropriateness of the costs from the standpoints of the university, the principal investigator, and NIH.

Committee Discussion

Dr. Fredrickson asked how much flexibility there was in terms of adjusting the items under administrative cost. Mr. Kirschenmann noted there were some constraints under Circular A-21, but with a good deal of latitude in what is permissible. The general standard is that costs are allowable if they directly benefit research, and a good deal of discretion and judgment is involved here.

Dr. Bondurant noted that the data for New York University show that over the three-year period specified, the indirect cost rate fell about one-seventh, but total research dollars from NIH to NYU increased about 20 percent. Thus, there is an absolute increase in the amount of money that went for indirect costs, while the rate declined. Dr. Bondurant wanted to know whether the rate fell because the cash flow increased. Mr. Kirschenmann responded that this was theoretically possible; however, he was not sure whether the indirect costs were prepared prior to a determination of how much the university would claim or whether the indirect costs were tied to the income generated. Dr. Wilson responded that universities cannot dump any costs they wish into indirect costs. She noted, for example, that, rather than assign use charges for equipment to indirect costs, one can write them off on a depreciation schedule or charge them as direct costs. However, to use either of the latter methods requires a lot more administrative effort, time, and funds. Under none of the methods does the institution get full recovery.

Mr. Kirschenmann noted that a university builds indirect costs around a total budget. If it is not recouping all of its costs, a number of options must be considered, because basically the university must be paid for direct costs incurred in order to support the research. Dr. Eyzaguirre reported on the frustrations of principal investigators as more and more of the grant money is eaten up by indirect costs and overhead. He said they feel they are being gypped--and NIH as well--particularly at State institutions where indirect cost monies go back to the State's treasury for general distribution rather than back, for example, to the particular university or laboratory that generated the money in the first place. These questions really needed to be discussed openly. That, said Dr. Fredrickson, is precisely the reason the Director's Advisory Committee has been examining these issues with all parties concerned.

Dr. Andrews said that the faculty perceptions are wrong about indirect costs. They are real costs, and that must be emphasized and reemphasized. He noted, for example, that Purdue spent $1 million for a P-3 laboratory and that none of the cost will come from project grants. Purdue places much money in renovating buildings and constructing new facilities (e.g., animal facilities) without being reimbursed for these through grants. Universities receive a great deal of money from the Federal Government; but for many things, such as facilities and equipment, they are having to expend their own funds or funds from other sources.

Mr. Hutt responded that universities need to plan their investments and not predicate their investments on future Federal dollars from research grants. Dr. Thier responded by noting the strength of the Federal commitment to research over the past 25 years and said it was in the national interest to have this research capacity. Thus, when the university builds a facility, the Government in effect has access to a resource it would not otherwise have had; consequently, the Government should contribute to it through research grants. Dr. Porter stated that universities can recover some of the cost by selling space to principal investigators and by charging it to their grants.

Dr. Brown observed that this discussion highlights a basic problem--that university administrators too often lack credibility with faculty in matters concerning indirect costs. He pointed out that at the May 1980 meeting of this committee, he was startled to hear highly respected university administrators making statements about indirect costs that he knew to be incorrect or at least very misleading. This was part of the motivation for his article in Science. He does not consider it reasonable, for example, to expect the faculty to believe that universities lose money on Federal research grants, so long as those same universities avidly seek such grants. He remarked that this credibility issue is one that needs to be squarely faced because it is an important aspect of indirect cost problems.

Dr. Ramey said that this adversary position stems from a number of problems facing the universities as the dollars run out and they must handle the commitments placed on them in the 1960s when universities expanded their faculties and student bodies to meet the Federal investment in research and medical training. Now universities with larger faculties and doubled student enrollments face severe retrenchment. Medical schools now have a cadre of tenured faculty, many of whom are not receiving grants and whose full salaries must be borne by the university. The tragic consequence of this is that young faculty cannot be recruited or retained, and cannot get into the system. The key issue is the nature of the Government commitment to the "monster" that it created.

Dr. Fredrickson responded that the Government is examining and changing a number of its commitments. But the focus should not be so much on commitment as on social needs, where there is a need to maintain the U.S. scientific capacity--especially, if one considers the Nation's need for increased productivity and an improved technological base. The basic philosophic issues on the nature of the future commitment are in fact being faced.

Dr. Fredrickson then turned to Mr. Kirschenmann and asked whether he would be willing to grade the various components of indirect costs as displayed in his tables. Mr. Kirschenmann said he would give the following rating based on his perceptions of how the Congress, the OMB, and the Federal Government generally view these items. First, use allowance for buildings and equipment and operation and maintenance--all get high priority, rating an "A." There are certain questions about the level of reimbursement for these categories. For example, should the allowance be based on historical cost (as is now stipulated by Circular A-21) or replacement cost? Research administration and general administration would rate a "B." There is less confidence for some committee work under research administration; this might rate a "C." Clearly, there is strong support for institutional review boards, EEO committees, and other Federally mandated areas. However, there is less confidence in such matters as faculty effort on budget committees, recruitment of graduate students, and the like. General administration rates quite high, but there is concern for paying part of the salary of the President or Vice-President; however, these costs are really insignificant, so there is not too much concern about payment here. Concerning library costs, a rating of "C" would be appropriate. He noted that in the past some Congressional committees have expressed concern about such support, and it has been suggested, for example, that Harvard should not be reimbursed for the Widener Library. Some have suggested that there should be no reimbursement at all, others that it should be part of the direct costs rather than the indirect costs. Departmental administration and student services rate a "D," "E," or "F." Those are the areas of primary concern, and we need a better sense of the rationale for reimbursement.

Consideration of Indirect Costs: Possible Approaches

Linda Wilson, Ph.D.
Associate Vice Chancellor
University of Illinois

Dr. Wilson said that the continuing debate over indirect costs had inspired attempts to design alternative approaches that might improve understanding, reduce friction, and equitably distribute the responsibility for reimbursement of research costs. She indicated that there is a basic lack of agreement among the concerned parties (the Congress, investigators, sponsoring agencies, audit policy officials, university administrators) as to what distribution of responsibility for costs of research is fair.

In considering indirect costs, it was important to recognize that the university environment is different from that in other organizations. In particular, universities have students, are involved with a joint product environment (research, service, instruction), and are oriented toward creativity and innovation. Also important were the changing perceptions of the faculty's role in institutional financial management--a consequence of increasing economic restraints. A fundamental question was the appropriate Federal role in supporting indirect costs of biomedical research.

With this as a general background, Dr. Wilson then specifically addressed the issue of indirect costs. Indirect costs have been rising at an alarming rate. Moreover, these costs are not very well understood. Can alternative approaches be designed that would assure adequate incentives and controls, yet leave research capacity undiminished? Dr. Wilson then examined a number of possible approaches to handling indirect costs. (See Attachment H for a more detailed analysis of the specific advantages and disadvantages of the options presented.)

1. Maintain the Status Quo: Recovery of Indirect Costs Within Present A-21 Limitations. This approach provides appropriate Federal audit for propriety, reasonableness, efficiency, and effectiveness; allows for diversity of institutions' organizational structure, management philosophy, and nature of the research portfolio; and allows consideration of the full cost picture by all concerned. However, under current procedures, some costs are not easily controlled or even visible. Moreover, disagreements about distribution of costs lead to audit hassles. Variations in rates among institutions are often challenged, and indirect costs appear to be under less control than direct costs.

2. Maintain the Status Quo With Improved Understanding of Indirect Costs. Current procedures would apply. However, separate rates could be identified for facilities and administrative costs to make them clearer. And more information could be provided to investigators, granting agencies, and the Congress about what indirect costs are, how they are calculated, why they vary, why they have increased, and how they are controlled.

3. Treat More Cost Elements as Direct Costs. This could be done as a requirement of the Federal Government, or by choice of the institution. It would increase the visibility and control for the principal investigator, study section, and institution, and provide truer cost analysis on a project-by-project basis. But for widely shared facilities and resources, it may sometimes be difficult to allocate costs accurately. Direct costing can be more costly to administer, is vulnerable to variations in practice among NIH Institutes and programs, and complicates long-term planning for research services. And Government requirements for consistent treatment of costs would necessitate significant revision in certain institutional budget practices.

4. Change the Mechanism for Reimbursement of Indirect Costs From a Project-by-Project Basis to an Aggregate Settlement. Under this arrangement, indirect costs would be calculated on an institution-wide basis and paid to the institution as an aggregate settlement rather than distributed to individual projects on a proportional basis. While this avoids the problem of inequities resulting from application of an average rate to projects that may deviate from the "norm," it would further diminish investigator participation in decisions that influence indirect costs and would pose some difficulties for the institution and the Government in budgeting for these costs.

5. Circumscribe Recovery of Indirect Costs. Recovery of certain elements of cost could be limited through definitional changes or through imposition of a ceiling on part or all of the indirect cost rate. Also, recovery could be limited to prospective increases in indirect cost rates or to some function of inflation and appropriations available.

6. Reduce Not Only the Reimbursement of Indirect Costs but Also the Costs Themselves. This is the most constructive approach, as it conserves resources without damaging the institution or the investigator. However, it would probably entail some reduction in research capacity, and may be difficult to accomplish. In implementing this alternative, institutions could develop new incentives for control of indirect costs, allow preselection of levels of service at different indirect cost rates, and improve productivity of services. The Government could simplify reporting requirements, apply a Fixed-Obligation Grant mechanism for most individual research project grants, delegate authority for all prior approvals to the principal investigator (except for change in scope, principal investigator, or institution), allow aggregation of related projects, and deregulate in some of the compliance areas such as affirmative action, FDA Good Laboratory Practices Act, and laboratory animal care.

7. Increase Productivity. This might be achieved by setting up incentives for development of shared instrumentation resources, or through a streamlined small grants program to encourage frugality and exploration of new ideas.

In conclusion, Dr. Wilson recommended consideration of the following as perhaps the most advantageous modifications in terms of reducing friction and introducing controls on the costs: (1) discontinue the award of retrospective indirect cost increases, (2) try the Fixed-Obligation Grant in the hopes that the reduction in administrative costs and the increase in flexibility for the investigator will have good payoffs in productivity and some reduction in indirect costs, (3) explore the wisdom of establishing the small grants program, (4) allow cost transfers or aggregation if the latter is necessary to avoid the artificial "pigeonholing" of research projects, (5) develop additional institutional incentives for reduction of indirect costs, and (6) improve mutual understanding of both indirect costs and incentives for their control.

In the longer term, the real need is to redefine the grant so that the relationship and the expectations of the parties are more clearly understood and the distribution of responsibility for the costs of research is a matter of genuinely mutual agreement. At the same time, significant moves to minimize regulation of higher education institutions in areas affecting research could contribute to a reduction in cost. The principle here is to specify performance expectations, but delete requirements for detailed process specifications.

Committee Discussion

Barbara Hansen, Ph.D.
Associate Dean for Graduate Studies and Research
School of Nursing
University of Michigan

Dr. Hansen said she had provided to the working group, for purposes of discussion, examples of institutional differences in determining direct versus indirect costs. (See Attachment I.) It is important, she believes, to maintain the visibility of these issues and to educate faculty, university administrators, and relevant Federal program and auditing officials. She noted that the working group must try to address these issues and develop recommendations specific enough to be tested and assessed in terms of their impact on the health research enterprise.

Recommendations must focus on several key areas. One of them is the impact of Federal regulations on universities, particularly in the areas of (1) animal and human welfare and safety, (2) the grant process itself, and (3) social programs such as EEO. Dr. Hansen felt that the balance was critically important here. She said that several NSF program initiatives might be considered, such as permitting charges to a grant 90 days before the start of a grant period. Other mechanisms developed by NSF permit budget transfers and lateral movement of funds among closely related research projects. She suggested trying to cut back reporting requirements, such as the cost-sharing reports. There was a need also to examine possibilities for reducing red tape and to develop a better understanding of the total cost of research.

Kenneth T. Brown, Ph.D.
Professor of Physiology
University of California (San Francisco)

Dr. Brown pointed out that there are at least two major problems (both alluded to earlier) concerning the Federal Government's policy on indirect costs. The first concerns how indirect cost rates are approved, especially by comparison with the rigorous three-step prospective review of direct costs by study sections, Institute councils, and NIH intramural personnel. Indirect cost rates are approved in the renegotiation process, and the review is largely retrospective. There would naturally be great reluctance to disallow, for example, indirect costs that result from salaried personnel already hired.

More important, Dr. Brown stated, it is not feasible, according to Federal personnel who conduct these negotiations, to determine whether any given item of indirect costs is justified as part of an efficient operation, or even whether it is needed at all. One can only determine whether the indirect cost items fall within accepted definitions. If a similar approval system were applied to research equipment, for example, an investigator could purchase any item he desired, providing only that he could later demonstrate that it fell within the definition of research equipment. He would not have to prove its value to his research project. This appears to be exactly the type of policy that is applied to indirect costs. In Dr. Brown's view this approach provides inadequate incentive to minimize indirect costs. In fact, it would appear to discourage efficiency and lead inevitably to a burgeoning and costly bureaucracy within the university. Under this policy, indirect costs will continue to climb.

The second problem Dr. Brown emphasized was that indirect costs, like inflation, feed upon themselves and are thus out of control. Institutions that have maintained low indirect costs will feel that they are not being treated equitably and will seek higher rates. Noting Dr. Wilson's assertion that she had never heard of an institution seeking higher rates for this reason, he said he could cite one. The University of California, his own institution, has recently been considering a requested increase of its negotiated indirect cost rate from 31 to 54 percent. One of the reasons is the desire to raise its indirect cost rate closer to that of most other institutions. In short, indirect cost rates are spiraling upward in a vicious cycle that must be broken, and the sooner the better. It appears that this can only be accomplished by positive measures, such as the regionally uniform and stabilized indirect cost rates proposed in his Science article (Attachment J).

Most inquiries into these important problems turn around the question of equity to the universities. In contrast to Dr. Thier, Dr. Brown seriously doubts that the current policy provides equity. Universities differ in their beliefs concerning the desirability, from the standpoint of overall educational policy, of seeking maximum indirect cost rates. And among the universities that do, there will inevitably be differences in the diligence and abilities applied in negotiating them. All of these factors will be translated into differences in indirect cost rates, which will thus be inequitable.

In view of these considerations, it is not at all clear that regionally uniform rates would be any less equitable than those under the current policy. Certain inequities, probably differing somewhat, would be expected to occur in either case. Indeed, it does not appear that equity considerations can or should be decisive. Dr. Brown believes that regionally uniform rates would offer many important advantages, which would solve or alleviate most of the serious problems that have developed.

Gaylord L. Ellis
Director, Division of Grants and Contracts
National Science Foundation

Mr. Ellis said that he had previously described NSF programs at the DAC meeting in May 1980. He was here to give a progress report specifically on the Association of American Universities-National Science Foundation experiment in redefining the project grant relationship. (See Attachment K for background information on the project contained in a letter from Mr. Thomas A. Bartlett of AAU to HHS Secretary Schweiker.)

Mr. Ellis reported that the experiment is now in Phase II. It began with nine schools and has now been extended to 12. What had originally been focused on a single discipline--chemistry--has now been expanded to most NSF programs. Thus, it has increased approximately 20-fold in scope, from a few hundred research projects to several thousand. The thrust of the experiment is to delegate to the university additional postaward authority to reduce the need for Federal paperwork requirements. The basic premise to be tested here is, Can the principal investigator and the grantee institution be given additional authority to manage research effectively, while providing assurance of accountability for the expenditure of public funds? This experiment does not change the NSF peer review system in terms of consideration of the proposals. The thrust is to delegate postaward controls to the universities in such areas as travel, equipment, preaward costs, no-cost extensions, and transfers among related projects. However, NSF still requires prior approval when there is a change of scope or of principal investigator.

Mr. Ellis said he had reported before on the NSF Master-Grant Program for aggregated awards to institutions. This combining of several approved grants, however, can be accomplished more effectively without using master grants. The concepts in the master grant have been put in the standard NSF grant. For example, principal investigators in the experimental program should be permitted to transfer funds among related projects. In conclusion, Mr. Ellis noted that NSF's evaluation thus far has shown that the experiment is a success, from the perspectives of NSF, the universities, and the principal investigators. It has reduced substantially NSF's paperwork requirements, though it has not done so for university administration. However, it is much easier for the principal investigator to get the necessary approvals at the university level than at the Federal.

Consideration of Indirect Costs: The Fixed-Obligation Grant

Linda Wilson, Ph.D.
Associate Vice Chancellor
University of Illinois

Dr. Wilson began by noting that she and Mr. Kelly had prepared a paper on the Fixed-Obligation Grant for presentation at the DAC meeting in October 1980. (See Attachment L for that proposal.) She noted that NIH had provided her with data indicating that in each fiscal year the average research project grant showed an unobligated balance of about 1.7 percent. The balances ranged from 1.5 to 1.9 percent. Unobligated balances at this level provide for approximately 226 additional grants. This represents about 4.5 percent of the 5,000-grant minimum called for in the NIH stabilization initiative. Thus it is a critically important factor.

Dr. Wilson noted that what we need now is a trial, taking two samples of research project grants--one where the Fixed-Obligation Grant would be the approach, and the other the current NIH approach. Over a period of one or two years, one could examine the budget activity and expenditure by class of objects to determine the impact. For 1974-75 expenditures, there was generally overestimation in personnel, travel, and patient care costs and underestimation in equipment and supplies. We would need new data for this trial, and particularly, to determine the unobligated balances remaining in the "control" group of regular grants. There would have to be a certain threshold. For example, the size of the average R01 grant in 1980 was approximately $85,000 in total costs; but 20 percent of the R01 grants were less than $50,000; 52 percent were less than $75,000; and 75 percent were less than $100,000. There would have to be an adequate mix in sizes of grants in the Fixed-Obligation Grants trial. Clearly, a most important aspect of this approach would be to delegate to the university and the principal investigator the responsibility for managing the project within the amount of the grant. This delegation would be made with certain specific understandings--for example, adherence to established institutional policies and federally approved indirect cost rates, the role of the principal investigator in controlling direct costs, the agency's role in changes in scope, PI, or institution, and unavailability of unobligated balances at the end of budget and project periods. (See Attachment L.)

Committee Discussion

Dr. Fredrickson opened the general discussion by noting that Mr. Kelly and Dr. Wilson had been working on the Fixed-Obligation Grant proposal as a result of the May 1980 DAC meeting, and that clearly there was a need to consider whether there should be a trial of this concept. Mr. Hutt inquired as to the purpose of the approach. Dr. Wilson said that the rationale and goals had been cited in the proposal presented at the October meeting of the DAC. (See Attachment L.) Mr. Hutt asked whether the universities would be able to get more dollars this way. Dr. Wilson responded that indeed they would, by virtue of a reduction in indirect costs; however, the costing process involved in indirect cost calculations would not be changed by the new grant. Under the grant NIH would provide a certain amount, and it would be up to the university and the principal investigator to decide how this should be allocated. It is not intended to set the grant at an amount higher than the research project grant.

Dr. Wu asked whether this approach would be used primarily for mission-oriented research rather than for basic research, where the outcome was problematical. Dr. Wilson replied that it could cover all research, even if the outcome could not be predicted. The investigator would be required only to provide a good technical report on the basis of the work done.

Dr. Fredrickson observed that the Fixed-Obligation Grant would reduce or eliminate time-and-effort reporting now required by the Federal Government. Dr. Eyzaguirre felt the approach would be particularly useful if funds could be carried over from one year to the next. Dr. McDermott thought the grant was a good idea, especially since it would remove issues of why the Government supports research, and would reduce the conflict between university faculty and administrators on the one hand and Federal program officials and auditors on the other. Dr. Thier said that this approach would, in effect, place the debate between faculty and administrators about indirect costs squarely at the university level. Dr. Brown commented that this would not solve the indirect cost problem generally, but would focus it more at the local level. Dr. McDermott agreed, adding that it would illuminate the nature of indirect costs for all parties at the university level and would be a good test of whether this approach could be used for all grants. Dr. Hansen said she was concerned about the impact of forcing the debate on university administrators and faculty. She believes, however, that now, with some of the revisions suggested by Dr. Wilson, the responsibilities are better defined and the conflict there will be minimal.

First Day: Afternoon Session

II. REPORT OF THE WORKING GROUP ON COOPERATIVE RESEARCH RELATIONSHIPS WITH INDUSTRY

Introduction and Overview

Charles U. Lowe, M.D.
Acting Associate Director
for Medical Applications of Research
National Institutes of Health

Dr. Fredrickson announced that Dr. Bennett was unable to be present, and therefore that Dr. Lowe, as Cochairman of the DAC Working Group, would report on the group's activities. Dr. Lowe noted that the mandate, membership, and minutes had been provided to the Committee members prior to the meeting. (See Attachment M.) He emphasized that the purpose of the working group, as cited in Dr. Fredrickson's mandate, is to examine issues related to patent rights and the protection of proprietary information where there is a commingling of government and industry funds for projects at universities and nonprofit institutions. It will provide for standards and procedures at NIH to govern peer review of proposals involving collaborative research, and will identify potential improvements in administrative requirements applicable to biomedical research funding. Dr. Lowe noted that the working group would be meeting over the summer and would report at the October DAC meeting.

Profile of Federal Agency Patent Policies

Charles U. Lowe, M.D.
Acting Associate Director
for Medical Applications of Research
National Institutes of Health

Dr. Lowe reported that the last of the working group meetings had provided the basis for a review of Federal patent policies and procedures. A paper was developed. (See Attachment N.) Dr. Lowe said that Federal patent policy had been governed by two Executive Orders, the first issued by President Kennedy in 1963 and the second by President Nixon in 1971. These policies generally were that inventions developed under Federal support belong to the Federal Government, but that the directors of agencies can change the policies to do the following: (1) give the patent to the inventor, or (2) give the inventor the right to license the patent.

In 1968 NIH established the Institutional Patent Agreements (IPAs), whereby the rights to the patents were waived to the organization where the invention had been developed, subject to a number of conditions and notice to the Government. In effect, the IPA served as a contract between the Department and the university, granting to the institution the first choice for patenting. If the institution chose not to proceed, the Government could do so. Generally, if the Government chose to do so, licensing was done through the National Technological Information Service (NTIS), in the Department of Commerce. NTIS has an office to manage patents the Government has acquired.

Dr. Lowe pointed out that each department and agency, because of the wide latitude in mission, had developed its own policies and regulations governing patent ownership within the framework of the two Presidential orders. All except Defense, however, retained march-in rights. In reviewing the agencies' activities, and especially because of the questions raised at the last meeting about whether any department or agency had ever invoked the march-in rights provision, Dr. Lowe had had each agency queried. As far as can be determined, no agency has ever taken a patent back under the march-in rights clause. However, Dr. Lowe added, industry--particularly the drug industry--is most concerned about this provision and regards it as a lien on property, diminishing the value of the patent.

Generally, the Government takes ownership of the patent automatically. NIH does not conform to this general pattern, but waives the rights to the organization where the invention was made. The military also has a different approach, as outlined in the patent review document. (See Attachment N.) In essence, the Defense Department specifies in its R&D contracts that all patents will belong to the contractor. No waiver is involved. Of approximately 30,000 Government patents, 1,500--or 5 percent--have been licensed by industry, and of those, 850 are NIH patents.

The major impact of the new Patent and Trademark Law Amendments is to statutorily mandate IPAs across the board, extending them to small business firms and to nonprofit organizations. Under existing Federal policy, they can also be extended to large business organizations through the discretionary power of agency heads.

Dr. Lowe outlined the policy objectives of the new law. They are to promote (1) utilization of inventions by small business organizations and universities, (2) participation of small business organizations in Federal R&D efforts, (3) collaboration between small business and nonprofit organizations, and (4) competition in utilization of inventions. Dr. Lowe concluded that the major focus now turns on regulations that will implement the law. They are to be released shortly for public comment, and their impact on NIH policies and programs will be considered by the working group during the summer meeting.

Committee Discussion

Peter Barton Hutt
Attorney-at-Law
Covington and Burling

Mr. Hutt stated that the morning discussions had focused on how to set up a system to get the best biomedical research to meet national goals and needs. The afternoon session was focusing now on the other side of the coin--namely, how to encourage commercialization of research results to benefit the public health. It was this latter area that NIH was now beginning to confront in a major way through this Committee.

Mr. Hutt said the history provided by Dr. Lowe illuminated very well the issues and the problems. Basically, as Dr. Lowe pointed out, there has not been a single Federal policy but a collection of them, depending upon agencies and departments. Therefore, it is difficult to apply these principles and practices to individual cases. They are too vague and general for business use, especially concerning rights under the circumstances involved.

Mr. Hutt stressed that the critical policy issues are (1) protection of inventions to permit commercialization, and (2) consistency of policy throughout the Government. The current policies did not meet those tests. It was policy on an agency-by-agency basis, not uniform, with very little collaboration. There were even differences among individual NIH Institutes. He noted that the National Cancer Institute, at the last meeting, had presented policies that permitted it to provide patents to large business organizations, while other Institutes cannot.

Mr. Hutt asserted that the Presidential orders were too general. They provided a policy that the Government owns patents, but offered an exception that swallowed up that rule--namely, that each agency could do as it wished regarding the waiver of patent rights. Then, the condition of march-in rights, in effect, swallowed up the discretion to waive patent rights by saying that the Government, in any event, could take the patent. All this resulted in an invitation to confusion.

Mr. Hutt referred to Dr. Lowe's comments to the effect that agencies have not invoked the march-in rights clause. At the last meeting, however, it was reported that patent rights had been voluntarily relinquished to NASA in approximately 100 instances. Mr. Hutt suggested that more likely the agencies state they will invoke the clause, and the inventor, in light of that threat, "voluntarily" agrees to turn over the patent. It is not a question of eliminating the clause, Mr. Hutt added, but of having clearer criteria for its use.

Mr. Hutt felt that the new patent law will not have a major impact on Federal agencies. It merely permits all agencies to do what NIH does now. Mr. Hutt felt that the working group is making progress on issues that NIH must now face regarding its relationship with big business. First, it is clear that this relationship is conditioned more by policy than statutory law. The Government, the Department, and NIH must decide how they wish to deal with industry. Second, there could be "business patent agreements" (BPAs), organized on an administrative basis, much as the IPAs were in 1968. And third, NIH could consider various options for handling patent rights and the protection of proprietary information vis-a-vis industry. Mr. Hutt added that NIH can handle proprietary information, as Dr. Gartland would point out later in describing the activities of the Recombinant DNA Program Advisory Committee, and further, that universities can develop sensible policies in this regard. The working group will review Dr. Andrews' excellent documents on how Purdue deals with proprietary information and patent rights.

Dr. Pings asked whether the new law provides for march-in rights and what conditions are set for their invocation. Mr. Hutt replied that the law does set a number of conditions but still leaves a great deal of discretion to the departments and agencies on how it should be administered and applied.

Implementation of Public Law 96-517 (Patent and Trademark Law Amendments)

Darrel J. Grinstead
Assistant General Counsel
Department of Health and Human Services

Mr. Grinstead opened by referring to the summary he had prepared of the issues under the law, the issues pertaining to the drafting of regulations, and the law itself. (See Attachment O.) He agreed with Mr. Hutt that the new law makes few significant changes in current HHS practices. It extends the mandate to small business organizations. The regulations, he said, will be published shortly for public comment in implementing the law, and those regulations will raise a number of issues for NIH.

One issue is whether there should be an oversight agency responsible for taking appeals for agency decisions on patents and also responsible to the Congress for implementation of the law. At present each agency handles these practices and policies separately. The advantage of an oversight agency would be uniform administration. The disadvantages would be procedural problems for each agency, with perhaps increased paperwork and less discretion.

A second issue is that of subcontracting. Small business organizations and nonprofit organizations or subcontractors retain the patent as if they were the primary contractor. The question is, What are the rights of subcontractors who are not eligible under the law, such as big corporations? The draft regulations suggest that the rights would be left with the subcontractor, whether or not it is a large corporation, and this policy would govern so that patent rights would not be used as part of the bargaining process for purposes of contracting.

Another issue that will need to be considered concerns invention reporting requirements. The requirement to disclose, elect, and file prior to submission of a manuscript for publication places university and nonprofit investigators in a dilemma. Should they pursue patent licensing and delay publication for an indefinite time or pursue publication without regard to patents? This is a serious intrusion into an investigator's traditional freedom to publish.

Mr. Grinstead pointed out that the major issue touched on by Mr. Hutt is that of march-in rights. The law provides that these can be invoked on the basis of health and safety needs, for example, or by the failure of the licensee to bring the invention expeditiously to the marketplace. As Mr. Hutt noted, setting standards here will be the key. We have none now, nor do we have explicit procedures governing march-in rights; and yet, without any generic rules or standards, cases have been coming and decisions made on a case-by-case basis.

It should be noted, said Mr. Grinstead, that when standards and procedures are set, there will probably be a great many more cases to handle because outside organizations will be more active in challenging patenting and licensing agreements, especially in the area of third-party rights. As Mr. Hutt proposed, procedures must be developed to follow up and monitor patents and licensing under them.

Committee Discussion

Frederick N. Andrews, Ph.D.
Vice President
Purdue Research Foundation
Purdue University

Dr. Andrews stated that universities would have had no difficulty implementing the law five or ten years ago, but since 1976, with the advent of genetic engineering corporations, the situation has changed. He noted that public universities like Purdue have been able to handle patent problems very well over the past 50 years; and for many of their schools, such as Agriculture, Pharmacy, Engineering, Medicine, and the like, Purdue has had a very good patent policy that fairly met the needs and rights of the University's faculty and the public interest. However, the climate since 1976 has changed, and there are problems for the universities. For example, inventors hope for sudden wealth, placing tensions on faculty and university regarding inventions developed there. Also, a new group holding master's degrees in business administration are rigorously recruiting scientists to form corporations with venture capital backing.

Dr. Andrews said that traditionally it has been rare for an invention to be developed in the university laboratory and taken directly to the market. Corporations should spend a good deal of money on additional research and invest substantially in development. It has been estimated that the average development cost of a new drug in 1980 was about $70 million. Now the picture has changed, with venture capital and the hope that recombinant DNA research techniques may provide for movement rapidly from the laboratory to the marketplace.

Dr. Andrews described Purdue's process with regard to patents and inventions. First, there has to be disclosure. The university patent committee evaluates whether there is likely potential for patents and considers the need of an investment to file for the patent here and abroad. If there is agreement, then an industrial sponsor must be sought out for licensing, and university rules developed to deal with it. Currently, Purdue is considering these processes. It seeks ways to meet the new challenges of the biological revolution, to keep the university inventor involved in the process, and to ensure collaboration among all parties--graduate students, faculty, university administrators, and industry.

There is a need to consider issues regarding public disclosure and patenting. Instances have arisen where Ph.D. examinations in molecular biology, formerly open to anyone, are now held privately in order to protect possible patent rights and proprietary information. There is also the question of commingling of funds and who will own the patent--the university, the inventor with his company, or industry that may have supported the investigator. These are difficult questions for the universities as well as the DAC working group.

Dr. Andrews concluded as follows: that he supports the business patent agreement concept; that requirements for reporting inventions are reasonable; and that march-in rights are necessary to protect the public interest. NIH must consider how it will handle patent rights developed by intramural personnel, especially foreign rights. He also approved the Congressional proposals to extend patent rights to large corporations conducting Government-supported research. (See generally the legislative reference material in Attachment P.)

Mr. Hutt referred to Mr. Grinstead's comments on the regulations concerning patent rights and use of licenses. He thought there would be no need for reporting to the Federal agencies unless complaints were filed, but feared that there might be requirements for extensive records and reports. He said he hoped it would be a minimal system. Mr. Grinstead responded that basically it will be up to the agencies, like NIH, to decide what really is needed, and he did not believe there would have to be extensive reporting.

Dr. Ramey asked how the allocation of rights would be determined, especially where there is commingling of funds between NIH and industry. What of an invention, for example, where the basic work was done on an NIH grant and the developmental work on an industrial grant? In that situation, who would get the patent? Mr. Hutt responded that this is an important issue, but basically not one for the Government, since the Government waives the rights to the university under the institutional patent agreement. It is an issue, as Dr. Andrews noted, for the university and industry, with the university primarily determining the policies.

Mr. Hutt added that this is not an issue for the working group concerned with the question of allocation of patent rights or royalties between university and principal investigator. Mr. Grinstead said the law mandates that there shall be a sharing of royalties, but sets no level, and the legislative history suggests that royalty rates should only be set if there is a compelling reason.

Dr. Bondurant agreed with Dr. Andrews that the law does not really take recognition of the biological revolution and the new factor of entrepreneurship affecting the universities. Dr. Pings stated that the law, primarily, was intended to provide incentives for universities and small business organizations to patent inventions, and as such, does not call for an extensive monitoring system. If records were required on each patent, the Government would have to keep track of 30,000 patents, of which only 1,500 are licensed. Care should be exercised to avoid, if at all possible, extensive or annual reporting. Dr. Fredrickson said that this is not a major concern, because we do not have the resources to use, even if we wished, and that we do not consider it critical.

Dr. Fredrickson went on to ask whether there were any Department standards on the commingling of funds. Mr. Grinstead replied that there were not, but if any Federal dollars are involved, then Federal policies apply--namely, that the university owns the patent and can deal with it as it sees fit. Dr. Fredrickson commented that the real problem in the future will be how to draw the lines--for example, in DNA research, with the principal investigator doing the work at the university on Federal and industry funds, and perhaps at the same time owning his or her own corporation. Mr. Grinstead reiterated that there are no rules and regulations on commingling, but that the matter could be considered for inclusion in the implementing procedures.

Dr. Bondurant noted Mr. Hutt's emphasis on the need for protection and certainty. Dr. Fredrickson affirmed that once standards have been set, there are limits that can be confronted. Dr. Pings noted that the new law is more concerned with incentives and increased productivity than with the Federal Government's share of the proceeds. Dr. Fredrickson agreed and emphasized that the major areas of concern are the commingling of funds and how that will be handled.

Dr. Ramey asked what consideration is being given the rights of the university investigator. Dr. Fredrickson replied that this is largely a university issue, since the institution will get the patents under the new law. Our major concern is the effect of these changes on the nature of the scientific system, particularly on the NIH system of peer review. Dr. Ramey reiterated her concern about the rights of the principal investigator or inventor. Dr. Andrews described the process at Purdue, noting that the patent policy committee determines the allocation of royalty in each case, and the principal investigator may comment on the recommendation before it goes to the responsible university official for action. Occasionally, the principal investigator appeals the recommendation and the appeals are heard and considered. Dr. Ramey asked what the rules are when the principal investigator does not wish to have a patent issued, as in the field of nuclear energy. Dr. Andrews replied that in such cases the inventor should keep his idea secret.

Dr. Lowe pointed out that the allocation issue is defined in the statute in the following terms. The first decision is whether the university wants the patent. If not, the second decision is whether the Government wants the patent. If again the answer is no, does the principal investigator wish to take up the patent? Dr. Pings stated that there is need for judgment and balance here. There are many ideas for which it is not practical to consider patents, because, as Dr. Andrews pointed out, the costs are significant for patent filing here and abroad.

Potential Impact of P.L. 96-517 on NIH Grants and Contracts Administration

Dr. Doris Merritt
Special Assistant to the Director
National Institutes of Health

Dr. Merritt referred to a brief statement prepared for this presentation. (See Attachment Q.) Specifically, the funding agencies will need to meet statutory reporting requirements and enhance their technical and administrative capabilities in relevant areas. She noted that the principal investigator is the critical element in inventions and patents. The law does not modify the inventor's behavior, and universities need to consider "preventive medicine"--to look at their policies regarding the rights and responsibilities of principal investigators and determine how to keep them better informed of the law and its implications for their work.

Universities may need to develop patent statements akin to tenure statements that lay out rights and responsibilities when faculty members come aboard. Especially critical here is the sharing of royalties, which must be spelled out ahead of time. Dr. Merritt pointed out that demands for clinical practice are having a deleterious impact on teaching and research, and that an aggressive patent policy may also have such an effect. Thus, concerned faculty members must participate in the development of administration.

Dr. Fredrickson asked Dr. Carl Douglass, Director of the Division of Research Grants, to comment on the role of study sections, if any, in regard to patents or proprietary information. Dr. Douglass replied that study sections do not deal with this matter and that there are no guidelines for them. Dr. Fredrickson noted, however, that a body which does have such rules and guidelines is the Recombinant Advisory Committee; and he turned to Dr. Gartland to report briefly on procedures developed by that committee to govern protection of proprietary and patent information.

Recombinant DNA Advisory Committee (RAC): Protection of Proprietary Information

Dr. William Gartland
Director, Office of Recombinant DNA Activities
National Institute of Allergy and Infectious Diseases

Dr. Gartland reviewed the development of the Recombinant DNA Guidelines from 1976 through 1980. He noted that the original Guidelines published in 1976 were silent regarding the private sector. In June 1980 the Guidelines were revised to include a special section devoted to voluntary compliance by industry. This supplement, Part VI, provided for registration of industry projects and protection of proprietary information. (See Attachment R.) The guidelines provide that only the RAC and relevant NIH staff shall have access to this information, and each member of the Committee must sign a document affirming adherence to U.S. Code and NIH guidelines governing review of proprietary information. In addition, all material must be kept in locked files under the personal control of the Committee member.

Of 25 Committee members, only one, who did not wish to participate, has declined to sign the statement. Six members do not have the material mailed to them because of the responsibility to maintain locked files. Over the past two years, the Committee has reviewed 20 submissions from five different companies, and the process has worked well. Dr. Fredrickson called on Dr. Susan Gottesman, an intramural NIH scientist who serves on the RAC, for her views on how the system is working. She said it has worked quite well, but there are problems. There is the responsibility to keep the information confidential when one sees problems with the science involved, the difficulty of keeping the files locked, and the constant need to isolate the ideas expressed in these proposals from one's own work.

Committee Discussion

Stuart Bondurant, M.D.
Dean, School of Medicine
University of North Carolina

Dr. Bondurant agreed with Mr. Hutt that the law will not have a great impact on NIH, especially since it basically codifies existing NIH policies. But there will be issues to be dealt with. Some universities will need to upgrade the quality and quantity of their management and, as Dr. Merritt has suggested, increase faculty awareness about the law and patenting generally. The policies may energize faculty interest to the extent that some faculty members may shop around for the most advantageous royalty conditions, especially in such areas as molecular biology. Dr. Bondurant did not see the law as increasing secrecy. That is determined more by the biological revolution and the huge influx of capital, which is the major issue for the universities, as Dr. Andrews had pointed out. Dr. Gartland's remarks show that proprietary information and patent rights can be handled reasonably well and will not have a significant impact on the grants and contracts process. Clearly, the law is not as important here as the financial interests fueled by the biological revolution, and that is where the interest and focus may lie for NIH and the academic community.

III. THE HYBRIDOMA: A CASE MODEL FOR EXAMINATION OF FEDERAL POLICY ISSUES, INCLUDING ALLOCATION AND USE OF PATENT RIGHTS BY GOVERNMENT, INDUSTRY, AND UNIVERSITIES

Introduction

Dr. Fredrickson opened the second day of the meeting by noting that yesterday's discussion had set the stage for today's examination of the implications of patent policies in regard to the hybridoma, another scientific aspect of the biological revolution. Dr. Fredrickson noted several issues of concern to this Committee that have appeared in the growing literature on government-university-industry relationships. He referred specifically to the statement by Harvard University President Derek Bok that had been provided to the Committee. (See Attachment S.) He also referred to recent articles in the New England Journal of Medicine on the commercialization of biomedical research. (See Attachment T.)

The Hybridoma: History and Potential Applications for Medical Research and Medical Practice

Matthew D. Scharff, M.D.
Chairman and Professor
Department of Cell Biology
Albert Einstein College of Medicine

Dr. Scharff reviewed the process of antibody formation and the uses of antigens and antibodies in research and clinical medicine. (See Attachment U for two articles provided as background.) Apart from the natural function of antibodies in the immune response, they have long been an important tool for investigators, who utilize their specificity to identify molecules or cells and to separate them from a mixture.

The antibody response to a typical antigen, however, is highly heterogeneous. Thousands of lines of lymphocytes can make antibodies that recognize specific antigenic determinants. When an animal is injected with an immunizing agent, it makes diverse antibodies directed against different determinants on a single antigen. Thus, conventional antisera contain mixtures of antibodies, lending to inconsistency of results in research and medicine.

This problem has not prevented the effective use of antibodies in diagnosis, investigation, and treatment of disease. But immunologists have sought methods of immunization that would produce large amounts of homogeneous antibodies. In 1975 Kohler and Milstein showed that mouse myeloma cells could be fused to normal spleen cells from immunized animals. The hybrid cell lines--"hybridomas"--grew continuously in culture. And they could be frozen, recovered, and injected into the peritoneal cavity of mice, where they grew and induced an ascites that contained large amounts of monospecific antibody. The principle could be extended to thousands of antigens.

In summary, the process comprises immunization, fusion, selection, cloning of the hybrids, producing the ascites, and freezing the cells for future use. This takes three to four months from beginning to end. The only limit on the amount of pure antibody available is the number of mice injected. These advances have exceeded the wildest dreams of immunologists, and are revolutionizing serology.

Dr. Scharff then stressed some benefits of the process:

- The development of pure antibodies from impure antigens;
- The ability to produce monoclonal antibodies conforming to specifications;
- The ability to produce unlimited amounts of antibodies;
- Homogeneity and predictability;
- The availability of antibodies as needed, lasting indefinitely;
- Low cost of production.

Dr. Scharff pointed out some persistent technical problems--for example, the difficulty of obtaining monoclonal antibodies against weak immunogens.

He noted that there were a total of 40 to 50 papers in this area a year ago and that now approximately that many are published each month. He summarized the applications as follows:

- Routine serology and tissue-typing (The market here is approximately $300 or $400 million a year; and with the use of hybridomas, it could reach $1 billion by 1985);
- Diagnosis and epidemiology of infections resulting from viruses, bacteria, and parasites;
- Identification of tumor antigens and refinement of the classification of leukemias and lymphomas;
- Mapped identification of functional subpopulations of lymphoid cells.

Future applications include:

- Passive immunization,
- Graft protection or tumor rejection,
- Manipulation of the immune response,
- Delivery of diagnostic or therapeutic agents.

In summary, basic studies throughout the world have resulted in a technology for the development of homogeneous antibodies in unlimited amounts that will last for indefinite periods. The technique has enormous clinical potential. Because the process is valuable to virtually all disciplines of medicine and science, shared facilities are rising in many universities to allow rapid transfer of information among scientists and industrial concerns. Industries are volunteering to support such facilities in return for first rights to inventions.

Federal Participation in the Development of the Hybridoma

Richard M. Krause, M.D.
Director
National Institute of Allergy and
Infectious Diseases

Dr. Krause briefly summarized Federal support for development of the hybridoma technology. (See Attachment V for relevant tables and diagram.) He said that during fiscal year 1980 NIH made approximately 553 awards in this area, totaling $48 million. It made 187 awards, totaling $16 million, for the laser cell-sorter, which is critically important in differentiating the monoclonal cells. Each sorter costs about $300,000. It can sort approximately 10 million cells an hour, revolutionizing the field.

Harry M. Meyer, Jr., M.D.
Director
Bureau of Biologics
Food and Drug Administration

Dr. Meyer spoke to the responsibilities of the Bureau of Biologics and the Bureau of Medical Devices. (See Attachment W.) He noted that the former is responsible for all hybridoma products used directly in human patients--e.g., for diagnostic and therapeutic purposes--and that Clinical Research is responsible for the investigation of new drugs. BOB is heavily involved in the use of hybridoma techniques for examining interferon, viruses, and the like. One product from the hybridoma technique has been approved by BOB, and one has also been approved by the Bureau of Medical Devices, which is responsible for *in vitro* diagnostic products not used in blood banks.

Dr. Meyer noted that the applications are many. They include the replacement or supplementation of existing products licensed by BOB--for example, the Rh-immunization globulin--or the manufacture of new products--for example, tagged tumor antibodies. There is less concern regarding regulation of the first group--replacement or supplementation--than in the area of new products. Here, one would need to meet the tests of safety and efficacy, and there would be no existing data, as there are when one is replacing a product already on the market. Much clinical research and information on safety and efficacy are needed before a product can be licensed. Dr. Fredrickson asked the status of hybridoma technology regulation in foreign countries. Dr. Meyer stated that he did not know, but commented that *in vitro* diagnostic products are not generally regulated.

Committee Discussion

Walsh McDermott, M.D.
Special Advisor to the President
Robert Wood Johnson Foundation

Dr. McDermott noted that the issues here are not of right or wrong, as in the area of safety committees or Institutional Review Boards, but rather concern for loss of the intellectual vitality of academic scientists. The key question is what effect this infusion of capital from the private sector will have on the academic climate, as discussed by Dr. Andrews. Dr. McDermott pointed out the enormous change in the economy and the complexity of the research effort. He added that 50 years ago, the interest from a $1 million grant from the Rockefeller Foundation had supported Wilder Penfield and supplied funds for his research. Today the University, with a budget of $500 million, gets 9 percent of its operating funds from investment income. Most of the remaining budget comes from the Federal Government.

Dr. McDermott stressed that we do not need a code of morals but rather a code of etiquette on how to handle this money. To get that code, we need to do a lot of talking about it at the university level, much as we are doing here at the DAC, for historically the rewards of science have not been money but more scientific advances.

Dr. Scharff raised some issues concerning patenting in connection with the hybridoma technology. He noted that laboratories can produce approximately 20 to 30 monoclonal antibodies a week; shared facilities, up to 100 a week; and all the products are potentially patentable. Current NIH guidelines require reporting patentable inventions, but it is impossible to report all monoclonal antibodies that might be patented. Basically, investigators report only potentially commercial antibodies to NIH. In response to Dr. Andrews' question about the number of patentable monoclonal antibodies that could be produced in a year by one laboratory, Dr. Scharff estimated 2,000. Dr. Andrews went on to remark that, at a minimum, it would cost $4 million to patent the laboratory's output.

Dr. Ramey asked how the drug firms are handling this technology. Dr. Scharff responded that they have not patented hybridomas. He went on to note that the commercial value of the technology lies in clinical practice, certainly not in scientific work. He did note, however, that commercially available hybridomas are enormously overpriced. He is concerned about the high markup, but hopes that the scores of competing firms and scientists involved in the competition will bring down the price.

Policy Questions for NIH in the Face of Emerging Biological Technology--Issues and Options

Charles U. Lowe, M.D.
Associate Director for Medical
  Applications of Research (Acting)
National Institutes of Health

Dr. Lowe referred to the series of questions he had developed that were given to the Committee members before the meeting. (See Attachment X.) He noted that NIH has responsibility as a Government agency to foster commerce. One way of doing this is to protect inventions so that inventors can exploit their products, increasing the commercial strength of the Nation. But this responsibility to encourage the patenting of inventions must be considered in light of the other responsibilities of NIH concerning research and health, an essential element of which is open communication. Another element is public examination of research grant applications through the peer review system. Dr.

Lowe stated that Committee discussion at this time centers on the reconciliation of these responsibilities. The new biology, however, presents us with a need to review our current policies and determine the changes we must make and their nature. He added that we are determined not to alter our mission, but rather to modify our patent policy and the way we do business.

Dr. Lowe went on to discuss the policy guidelines being considered by the U.S. Patent Office in light of the Supreme Court's decision to permit patenting of these biological inventions. Finally, he reviewed the items in his paper (see Attachment X) concerning (1) policies on invention reporting, patenting, and development; (2) policies on distribution and deposit of cell lines; and (3) policies affecting the peer review process in the face of commercial involvement of investigators.

Committee Discussion on Policy Issues:
Invention Reporting, Patenting, and Development
Distribution and Deposits of Cell Lines
Peer Review Process and Commercialization

Ronald W. Lamont-Havers, M.D.
Director for Research Policy
and Administration
Massachusetts General Hospital

Dr. Lamont-Havers opened with the observation that 25 years ago there had been a great deal of concern about the infusion of Federal funds for biomedical research at the universities. Ultimately the system worked out well. Today we are facing similar concerns over private funds coming to the universities for health research. The Massachusetts General Hospital (MGH), anticipating this, began work early in the 1970s to develop guidelines for its relationships with industry, particularly in the area of technology transfer; and policies were developed regarding patenting of inventions and consulting. MGH set up an Office of Technology Administration, headed by a patent attorney, to assist in this area.

Dr. Lamont-Havers outlined the agreement of MGH with the Hoechst Company, of Frankfort, Germany, to establish at MGH a department of molecular biology. Much has been written about this agreement in the press. (See Attachment Y for the agreement and article.) Dr. Lamont-Havers stated that Hoechst was not concerned with the ownership of inventions. The company's leadership promoted the agreement to obtain access to developments in molecular biology in the United States. Therefore, typical problems with secrecy, publications, and the like do not apply. The company believes that the existing MGH patent and consultant policies are appropriate as a framework for the agreement. Dr. Lamont-Havers added that without these policies in place, it would have been much more difficult to get the agreement so quickly.

Dr. Fredrickson asked whether the molecular biology department created under the Hoechst agreement will get NIH funds. Dr. Lamont-Havers responded that if Hoechst does not support a particular research project, the investigator can seek outside funding. Collaborative arrangements with NIH grantees will continue if the program is project-oriented. Dr. Raub asked whether the company would have the right of first refusal to fund a project proposal. Dr. Lamont-Havers responded that the company is really buying knowledge and an opportunity for training its people--four each year at MGH.

Dr. Goldberger asked whether those working in the department might consult with other firms. Dr. Lamont-Havers answered that this was a key issue and that there would be no general policy here; that each case would be reviewed individually, and Hoechst had agreed to this approach. Dr. Fredrickson asked how the hospital will make these decisions. Dr. Lamont-Havers reiterated that the process is in place governing patents and consulting. A committee of hospital trustees acts in this regard, with mechanisms through the Office of Technology Administration. Dr. Fredrickson responded that processes will be needed to monitor scientists in the department of molecular biology before they may consent to do work for any company other than Hoechst. Dr. Lamont-Havers agreed that these would have to be developed, but he was confident that existing processes and mechanisms would work here as they have for scientists who have received support from other industrial concerns. Under the Hoechst agreement, MGH retains title to the patent and the company maintains the right to an exclusive license.

Dr. Wilson noted that this agreement seems to afford a good deal of stability and ease of administration for MGH because they only have to deal with one company, rather than several companies under different agreements. Dr. Lamont-Havers agreed. There will be approximately 100 people in the laboratory, and $5 million will be committed annually over a 10-year period.

Melvin Cohn, Ph.D.
Fellow
Salk Institute

Dr. Cohn explained that he was at the meeting because he runs a cell bank and a cell distribution center. The cell bank began 25 years ago under a grant from the Allergy and Infectious Diseases Institute. It has evolved into a center for standards of purity of hybridoma cell lines and a source of expertise and technical information as well as a repository for cells. Its priority is to serve as a cell repository and to validate cell lines. He noted that there were more and more referrals preliminary to patenting, where deposit in a cell repository was necessary. Eventually, he said, the center declined to accept a cell line unless it could be sent out to other principal investigators, and this policy has proved sound.

Dr. Cohn said that the role of NIH is to support excellence in basic research, and it has done this extraordinarily well. Industry supports research but, with rare exceptions, is not oriented toward basic research. Industry must be goal- or mission-oriented. There are certain exceptions, such as the Basel Institute in Switzerland and the Pasteur Institute in France. He noted that publication of research results to validate an investigator's findings is critical to NIH support, and publication automatically makes information available to all scientists. In Dr. Cohn's view, patents do not generally prevent this. Indeed, he routinely sends out, for all cell lines deposited, a statement that they cannot be used for patenting and commercial purposes unless the original principal investigator approves. Dr. Cohn feels that NIH should stay out of the business of patenting, allowing the grantee institutions to make their own patent policies. He believes this system would work well, as it has in other areas, with general NIH guidelines and discretion at the local level.

Dr. Fredrickson asked whether patenting and the infusion of private money is placing strains on academic science and basic research, and whether profit issues are creating a problem. Dr. Cohn responded that, from his perspective, it is a minor problem, not a major one. In response to questions from Dr. Fredrickson and Dr. Scharff, Dr. Cohn said the repository stores altogether about 150,000 cell lines and sends out 2,500 to 3,000.

Thomas H. Adams, Ph.D.
Vice President for Research
and Development
Hybritech, Inc.

Dr. Adams stated that Hybritech was incorporated two and a half years ago under a $13 million investment from a venture capital firm and the endowment funds of three major universities. The company has 90 employees, 50 of whom are scientists. One of their products was the first approved by the Bureau of Medical Devices, as mentioned by Dr. Meyer. The company's work has three phases: first, in vitro diagnostic work; second, in vivo diagnostic work; and third, the use of antibodies for treatment.

There are several therapeutic possibilities--for example, drug-carrying antibodies to serve as a "magic bullet" against a disease. Dr. Adams remarked that he and Mr. Birndorf, his associate, had just returned from Europe and Japan. It is clear that the United States is one or two years ahead of any other country in this field. Thus, patents are important in protecting our position. He noted that, given the potential for billions of cell lines, virtually half of the country's GNP could be used just to patent all the hybridomas. While less than one percent of monoclonal antibodies will have any clinical utility and much work needs to be done, the future is great.

Dr. Fredrickson asked whether industrial support would be available for purification, characterization, and utilization of the antibodies. What is the role of industry vis-a-vis NIH? Dr. Adams responded that Hybritech supports clinically oriented research along these lines in several universities. Dr. Fredrickson remarked that at the previous meeting we had discussed drug development and the problem of funding research on "orphan drugs"--i.e., those with small markets. Would this model or analog apply here? Dr. Adams replied that the analog is apt here as well.

Dr. Lowe asked whether there was a conflict of interest for universities with investments in Hybritech. Dr. Adams thought not, because these investments are made by the trustees from the endowment funds. Dr. Fredrickson asked whether Hybritech attached conditions to its support of university research, particularly in terms of patents or publications. Yes, Hybritech negotiates agreements, said Dr. Adams, under which terms will be set for patent rights, licensing, and a range of royalty rates. To another question from Dr. Fredrickson, he responded that Federal funds in the laboratory complicate the problem, especially when they place a cloud on possible exclusive licensing by a firm. Dr. Adams added that this does not inhibit funding for his firm, though it may for larger corporations.

Dr. Goldberger asked whether investigators under support from Hybritech or within the company may share information with their colleagues. Dr. Adams replied that they may. Dr. Bondurant then asked whether there were any circumstances when they are not allowed to do so. Yes--for example, when an antibody is directed against an antigen that is in the public domain; they may then restrict distribution of the antibody. Dr. Cohn asked for examples of hybridomas created by Hybritech, and Dr. Adams listed several in the process of development. Dr. Fredrickson asked whether any questions need to be resolved now by the Federal Government to forestall problems in the growth of this industry. Are there any unresolved issues? Dr. Adams replied that the absence of a clear policy on the part of VA hospitals with regard to patent policy was the only major problem.

Dr. Lamont-Havers referred to Dr. Lowe's concerns about the impact of proprietary information and private capital on the peer review system. What problems might there be? Dr. Lowe stated that traditionally NIH has supported academic science, and there has been a distinction between profit-making science and academic science. Now industry is turning to support for basic research, much as it did after World War II. Thus, the study sections will be making judgments on the work, and will perhaps be influenced by the motive of the investigator: Is he working primarily for the development of knowledge or the development of capital? Judgment may shift from the basis of merit to the intention of the scientist, with priority scores affected negatively because of perceived industry connections. Dr. Lamont-Havers noted that this was indeed a problem from his viewpoint and that of some principal investigators, who may be reluctant to cite possible proprietary aspects of their research grant. Dr. Douglass noted that this question had been raised recently in a study section.

Dr. Scharff stated that NIH, as Dr. Merritt had pointed out, must educate principal investigators regarding patents. He added that he had learned something from attending this meeting--namely, that cell lines must be deposited in repositories before being patented and, therefore, must be made available for distribution. Dr. Lowe pointed out, however, that a cell line that has not been patented may be treated almost as a trade secret.

Dr. Fredrickson concluded the meeting by noting that the discussions had been exceptionally helpful in building on the work of the Committee over the past year and a half and should provide an exceedingly useful agenda for the work groups over the summer. He would report at the next Committee meeting, scheduled for October 1-2, 1981. With that, the meeting concluded at 12:15 p.m.

Respectfully submitted,

Joseph G. Perpich

Joseph G. Perpich, M.D., J.D.
Executive Secretary

National Institutes of Health
Bethesda, Maryland 20205
August 30, 1981

[32.45]

ATTACHMENTS

A (1) Members and (2) participants, NIH Director's Advisory Committee, Meeting of June 8-9, 1981. (3) Letter of invitation.

B Membership List, National Academy of Sciences Committee on Relationships Between Universities and the U.S. Government.

C Gutowsky, H. S., "Federal Funding of Basic Research: The Red Tape Mill," Science 212:636-641, 1981.

D Distribution of NIH Obligations, 1980.

E (1) Mandate, (2) Membership List, and (3) Minutes of DAC Working Group on Costs of Biomedical Research, 3/17/81 and 5/4/81.

F Report by the Comptroller General of the United States: Indirect Costs of Health Research--How They Are Computed, What Actions Are Needed, July 27, 1979.

G (1) Memorandum of April 20, 1981, from Henry G. Kirschenmann, Jr., to Task Force on Costs of Biomedical Research. Indirect Cost Rates With Component Breakout at 39 Colleges and Universities, for (1) One Year, (2) Three Years. (2) Checklist of Faculty Administrative Activities Which Universities Considered Reimbursable Under OMB Circular A-21.

H Possible Approaches to Handling Indirect Costs, by Linda S. Wilson.

I Examples of Possible Areas for Discussion Re Institutional Differences in Determining Direct vs. Indirect Costs.

J Brown, Kenneth, "Indirect Costs of Federally Supported Research," Science 212:411-418, 1981.

K (1) Letter of May 7, 1981, from Newton O. Cattell to Donald S. Fredrickson. (2) Letter of May 5, 1981, from Thomas A. Bartlett to Secretary Schweiker. (3) Redefining the Project Grant Relationship: An AAU-NSF Experiment, by Robert D. Newton.

L (1) Fixed Obligation Grants. (2) A New Funding Instrument--The Fixed Obligation Grant, prepared by Linda S. Wilson in consultation with James Kelly.

M (1) Mandate for Working Group on Cooperative Research Relationships With Industry. (2) Membership List. (3) Minutes of Meeting, 4/20/81.

N A Review of Federal Patent Policies and Procedures.

O (1) The Patent and Trademark Amendment Act of 1980 (P.L. 96-517).
(2) Analysis of P.L. 96-517 Regulation Drafting Issues, April 17, 1981.
(3) P.L. 96-517.

P Legislative Reference Material. (1) Patent and Trademark Amendment Act of 1980 (P.L. 96-517). (2) Orphan Drug Bill (H.R.1663). (3) Patent Term Restoration Act of 1981 (S.255, H.R.1937). (4) R&D Tax Credit Incentive Bills. (5) Small Business Legislation.

Q Impact of P.L. 96-517 on NIH Grants and Contracts Administration.

R Handling of Proprietary Data in Commercial Proposals for Recombinant DNA Research.

S Bok, Derek. "Business and the Academy." Harvard Magazine, May-June 1981, pp. 23-35.

T (1) Culliton, Barbara, "Biomedical Research Enters the Marketplace," New England Journal of Medicine 304:1195-1202, 1981. (2) Davis, Bernard, "Profit Sharing Between Professors and the University," New England Journal of Medicine 304:1232-1235, 1981.

U (1) Yanchinski, Stephanie. "Where Next for Monoclonal Antibodies?" New Scientist, April 9, 1981, pp. 102-104. (2) Diamond, B. A., D. E. Yelton, and M. D. Scharff. "Monoclonal Antibodies: A New Technology for Producing Serologic Reagents." New England Journal of Medicine 304:1344-1349, 1981.

V Federal Participation in the Development of the Hybridoma. Diagram of Laser Cell-Sorter.

W Requirements for Licensure of In-Vitro Diagnostic Products Prepared by Hybridoma Technology.

X Patent Policy Development for NIH Required by New Biotechnology.

Y (1) MGH Press Release of May 19, 1981, With Agreement Between MGH and Hoechst AG for the Establishment, Operation, and Financing of a Department of Molecular Biology. (2) Knox, Richard A. "German Firm, MGH, in $50m Research Pact." The Boston Globe, May 20, 1981, p. 1.

MINUTES OF THE
44th MEETING OF THE ADVISORY COMMITTEE
TO THE DIRECTOR, NIH

October 1 and 2, 1981
National Institutes of Health

COSTS OF BIOMEDICAL RESEARCH
and
GOVERNMENT-INDUSTRY RESEARCH RELATIONSHIPS

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ADVISORY COMMITTEE TO THE DIRECTOR, NIH

Minutes of the 44th Meeting
October 1-2, 1981

Prepared by
Joseph G. Perpich, M.D., J.D.
Executive Secretary

The 44th meeting of the Advisory Committee to the Director, NIH (DAC), was held on October 1 and 2, 1981, at the National Institutes of Health, Bethesda, Md. Dr. Thomas Malone, Acting Director, NIH, chaired. (See Attachment 1 for list of members and participants and the letter of invitation.)

First Day: Morning Session

Introduction

Dr. Malone pointed out that the agenda for this meeting reflected the evolution of the Committee as a policy forum for issues of key importance, not only to NIH but to the larger health research community, various Federal Departments and agencies, the OMB, and the Congress. He stated that the meeting thus represented an important stage in the Committee's examination of the relationships between government, university, and industry in the support of health research.

Since the last meeting in June, a number of significant changes have occurred at NIH. The most important is that on July 1 Dr. Fredrickson resigned as the Director, NIH, after six years of administering a major national enterprise. His grace and admirable style under pressure and in achievement, his notable scientific contributions, and his gifted administration during periods of difficulty and retrenchment have left their mark on the agency as a whole and have deeply impressed those who worked closely with him.

Dr. Fredrickson's qualities of science leadership were particularly evident in his work with the DAC. Dr. Malone had participated with Dr. Fredrickson in these proceedings and appreciated the practical gains that can be made through such an approach. The DAC cannot solve major problems, but it can initiate action in the right direction to remove some of the obstacles to effective cooperation in health research among the major sectors.

Dr. Malone reminded the Committee that Dr. Fredrickson had established the Working Group on Costs of Biomedical Research to examine options for treating indirect costs of federally sponsored health R&D at academic institutions and to simplify administrative requirements in Federal funding. As Dr. Fredrickson had noted, the Government and the universities are moving into an era of constrained resources, and pressures will surely grow to reduce indirect costs, which have risen faster than direct costs. Consequently, it is important to try to understand better the nature of these costs and to consider ways to contain them. Also, it is clear that strains in Government-university relationships have arisen as a result of pressures for accountability--epitomized by the recent revisions of OMB Circular A-21, "Cost Principles for Educational Institutions."

The Working Group, in a series of meetings, has analyzed the costs and administrative mechanisms involved in Government-sponsored research, including Circular A-21. It has examined a proposal for a "Fixed-Obligation Grant"--as an alternative to the present cost-reimbursement agreements. It has also assessed other potentially useful changes aimed at "deregulating" the system of research support. The proposed alternatives and recommendations of the Working Group are contained in its interim report.

Dr. Malone described the Working Group on Cooperative Research Relationships With Industry, created by Dr. Fredrickson to address issues relating primarily to patents and to private sector support for biomedical research. Although the Working Group was charged with the broad responsibility of assessing the impact on NIH administrative and review procedures of the newly emerging relationships between universities and the private sector, it chose to focus on the recently enacted Patent and Trademark Amendments Act (P.L. 96-517) and its implementing regulations.

Dr. Malone summarized the policy objectives of P.L. 96-517:

- To use the patent system to promote the utilization of inventions arising from federally supported research and development;
- To encourage maximum participation of small business in Federal R&D efforts;
- To promote collaboration between industry and universities;
- To ensure that inventions made by small businesses and nonprofit organizations are used in a manner to promote competition; and
- To minimize the cost of administering policies in this area.

In its deliberations the Working Group had two objectives: (1) to develop suggestions for inclusion in the Department's comments on the OMB regulations and (2) to recommend guidelines for NIH to issue to its grantees and contractors. The Working Group was particularly concerned that implementation of the new law proceed in such a way as to ensure maximum flexibility and minimal administrative burden for NIH grantees and contractors, particularly with respect to reporting requirements; to avoid disruption of the academic research environment; and to promote increased research innovation and commercialization, consistent with Congressional intent and limited only by statute or Federal policy.

The work of the DAC on these major national issues has enjoyed strong support from Secretary Schweiker, from Assistant Secretary Brandt, and more recently from the President's principal science advisor, Dr. George Keyworth.

Dr. Malone expressed pleasure that Dr. Brandt was the keynoter for the first day of the Committee meeting. He briefly reviewed Dr. Brandt's background, noting his experience in university health research administration and his doctorate in biostatistics. Dr. Malone added that Dr. Brandt has been encouraging in his support of the ongoing mission and program strength of NIH during this very difficult period of economic constraint. Dr. Malone acknowledged Dr. Brandt's help to him since assuming the Acting Directorship of NIH.

Health Research Perspectives of the Assistant Secretary for Health

Edward N. Brandt, Jr., M.D., Ph.D.
Assistant Secretary for Health

Dr. Brandt opened by noting that Dr. Fredrickson had kept him informed of the Committee's work. He was pleased to see its continuing progress under Dr. Malone, as Acting Director. Dr. Brandt said the process for selection of an NIH Director is well under way, but he could not comment about candidates because the Directorship is a Presidential appointment, to be announced by the White House. He mentioned the great respect he has had for NIH, both as a university executive and researcher and as Assistant Secretary for Health. NIH and its contributions are recognized as providing world leadership for biomedical research, and it represents one of man's crowning attributes--the ability to accomplish much through increased knowledge.

Dr. Brandt outlined three major Public Health Service objectives with which he has been dealing.

The first, reduction of Federal spending to control inflation, is the highest priority of the Administration.

The second is reevaluation of the Federal role in medicine and health. For example, the Public Health Service has operated 8 hospitals and 27 clinics throughout the country. With budget retrenchment, these kinds of services can be handled more appropriately at the State or local level. Further, functions such as those of Professional Standards Review Organizations (PSROs) are best performed by the professions through self-policing mechanisms.

The third priority is the new federalism initiated under President Reagan. For the Public Health Service this has meant implementation of the block grant concept. Dr. Brandt has been pleased with the response of the States to these block grants. All 50 States have joined in taking over maternal and child health services. Forty-nine have agreed to join the prevention block grant, and some are also joining the mental health block grant. He is confident that within the year the States will have excellent planning at the local level for delivery of these programs.

Dr. Brandt then turned to his and the Service's views on objectives for research. He noted that the Federal role is important in the support and stimulation of basic research, but it may not be exclusively a Federal role. There must be a reasonable relationship with industry and voluntary associations, and thus the DAC's work on cooperative research relationships with industry is particularly timely.

He outlined several questions that will constitute an agenda for the next NIH Director: How to set priorities with constrained funds? How to involve the NIH community and the public in determining those priorities? How to set the level of support and where to increase the effort? How to involve the academic community?

Dr. Brandt added that NIH has been extremely successful in the past, but will be tested in the future. The relationship between support for intramural and extramural research will need to be closely examined. He commented that Dr. Fredrickson's article in the New England Journal of Medicine (304:509-517, 1981) had raised the issue of stability for the NIH mission and programs, and the question will be, Stability at what level? Is the current projection of 5,000 grants and 10,000 trainees the correct proportion? And what should be the level for the rest of the NIH programs, such as research resources and centers, research applications, and technology transfer? Is the present mix appropriate or should it be different? These are the kinds of issues that will need to be faced by the next NIH Director, Dr. Brandt, and Secretary Schweiker.

Committee Discussion

Dr. Wilson asked whether consideration had been given to putting the research programs of the Public Health Service under a block grant. Dr. Brandt replied that this would only be done for research oriented toward delivery of specific services and programs, such as those in the prevention area. He cited the success of the measles immunization program. In 1970 there were approximately 500,000 cases, and more recently only 2,400 cases. Prevention is a key objective of the Public Health Service in concert with the States.

Dr. McDermott asked what the Federal Government's role would be in health care planning. Even with decentralization there would still be need for Federal guidance. Dr. Brandt said there would be Federal guidelines, but by and large the intent is to allow the widest discretion possible at the local level, because that is where the services are needed and the local determinations can best be made.

Dr. Hansen wanted Dr. Brandt to comment further about public and scientific input in developing research priorities, citing the HHS health research planning process and the principles developed over the past three years. Dr. Brandt said that such a forum might be considered in examining health research strategies for the '80s.

Dr. Bondurant wondered whether Dr. Brandt's perspective might have changed--from that of a university administrator to that of the Assistant Secretary for Health--on certain NIH strategies: for example, the number of grant-supported trainees and other NIH programs. Dr. Brandt replied that he now favors a different process for achieving the goals, though the goals will be the same. He realizes that the process is far more complex than he had thought when he was at the University of Texas.

Dr. Andrews cited a tremendous current shortage in the computer sciences and observed that universities cannot recruit faculty members. How should support, particularly in the shortage areas, be handled by the Federal Government? Dr. Brandt noted that it is critical to determine where the needs will be 10 to 20 years from now and how to provide support in those particular areas. We need a long-range view in setting priorities. Obviously, this is a major concern for the next NIH Director.

Dr. Bondurant asked how the emphasis on competition among health care insurance carriers would affect medical training, particularly of clinical investigators. He was concerned that with increasing competition, training would become severely impaired, as teaching and support for investigators could not be provided through third-party carriers. Dr. Brandt acknowledged that there continues to be a problem in attracting clinical investigators. Here, there is need for long-range planning, and he is considering how to induce more young investigators into clinical research. He will welcome suggestions for resolving this problem.

Dr. Porter wanted to know whether there was any possibility of providing intramural support of clinical investigation at universities around the country as well as at NIH. Dr. Brandt said no such plans were being considered. The issue here is the appropriate balance of support between NIH intramural and extramural programs.

Dr. Malone asked Dr. Brandt to comment on his priorities and those of the Secretary in the area of prevention and the relation of research to those strategies. He also asked for Dr. Brandt's thoughts on the general issue of Departmental policies concerning fraud and abuse in research programs.

Dr. Brandt reiterated the high priority he and the Secretary give to the prevention initiative. There is a strong commitment to make prevention a major part of the Public Health Service agenda. The approach is three-pronged. First, the knowledge base, recognized as incomplete, is being carefully reviewed. Fifteen major categories are cited in the PHS prevention strategy document Promoting Health/Preventing Disease: Objectives for the Nation. Second, there is an implementation plan involving voluntary, professional, and Government organizations, and emphasizing prevention in such areas as alcohol abuse and maternal health. Finally, PHS will cosponsor a symposium with the AMA and AAMC to develop means for more effective teaching of prevention strategies as part of the existing medical school curriculum.

Dr. Brandt agreed with Dr. Malone that fraud and abuse are not a major problem in the scientific community. The isolated instances that must be dealt with attract an inordinate amount of attention. The academic community and those who fund the research must address the issue head on. It is not the intent of the Government to set up a vast monitoring system, but the issue cannot be ignored.

Citing a recent article in the New England Journal of Medicine (Perry, D.R., D.R. Challinor, and R.J. Oberst, NEJM, 305:320-324, 1981), Dr. Sullivan asked what impact economic constraints and diminution of Federal support would have on those institutions that are not research intensive and yet conduct health research. In effect, what will happen to the smaller universities and colleges? Dr. Brandt noted that this is a particularly important issue. He said it is meaningful for all institutions, large and small, to participate in research, provided they are productive. Support of excellence has to be the standard, but the research funding should permeate the entire academic community.

Dr. Brandt concluded by thanking Dr. Malone for the opportunity to address the Committee and reiterated his keen interest in its work.

I. DAC SUBCOMMITTEES: COMPLETION OF INTERIM REPORTS OF THE WORKING GROUPS

Dr. Malone announced that the Committee would divide for the rest of the day into two working subcommittees, each responsible for review and revision of one of the Working Group interim reports, which would be considered by the full Committee on the following day. Agendas had been prepared for each subcommittee to ensure careful consideration of the key issues raised in the respective reports. Dr. Malone sought from the Committee a sense of what actions the Committee or a Working Group should continue and where it might be appropriate to defer to actions initiated in a larger sphere--for example, by the National Academy of Sciences or some similar body. He hoped that the meeting would produce a blueprint for action that might be considered by the NIH Director, Institute Directors, and advisory committees and, where appropriate, by the Public Health Service and the Department. The Committee as a whole was then adjourned for the work of the two subcommittees.

Minutes of the proceedings of the Subcommittee on Costs of Biomedical Research were prepared by Richard Giza, Executive Secretary for the Working Group on that subject. (See Attachment 2.) Minutes of the Subcommittee on Cooperative Research Relationships With Industry were prepared by Dr. Michael Goldberg, Executive Secretary for the respective Working Group. (See Attachment 3.)

Second Day: Morning Session

Research Perspectives From the Director,
Office of Science and Technology Policy
George A. Keyworth II, Ph.D.
Director
Office of Science and Technology Policy

Dr. Malone noted that yesterday's session had been opened by Dr. Brandt and that we were fortunate to have as today's keynote speaker Dr. George Keyworth, Director of the Office of Science and Technology Policy (OSTP) and Science Advisor to the President. Dr. Malone referred to Dr. Keyworth's training at Yale and Duke and to his service as a physicist at Los Alamos.

Dr. Keyworth said that the National Institutes of Health was the first research agency he had visited after assuming his responsibilities as Director of OSTP. He had been impressed by NIH before coming to Washington and is even more impressed since he has learned more about it. In his view, it is the model for other Government research agencies. Its total commitment to excellence in science and its leadership and management have been unparalleled.

Dr. Keyworth assured the Committee of the President's strong commitment to science, as evidenced in his budget decisions for FY 1982. Dr. Keyworth noted that as the effects of the President's economic recovery program become apparent, a firm science base will be increasingly important. The President's first priority, however, is economic recovery and control of inflation. To meet this priority, there have to be constraints and, indeed, cutbacks in all domestic Federal programs, and science and technology must share in these cuts.

Dr. Keyworth went on to emphasize that there is a legitimate and necessary Federal role in the support of science, with basic research as a priority. Dr. Keyworth noted the difficulty in defining basic research. Those in Government seem to view it as high-risk and long-term, with broad societal but little commercial payoff. But whatever the definitional problem, there is a commitment to Federal support. The universities, as centers of research excellence, have a key role here in maintaining the quality of the research environment. Federal dollars produce strains in that Government-university partnership. Thus, the DAC's examination of the Government-university partnership and skyrocketing indirect costs is especially important. Dr. Keyworth anticipates that the results will provide important policy advice to the Federal Government at all levels.

The President has a keen interest in the Government-industry relationship as well. Clearly, there is a greater responsibility in the industrial sector for applied research and its development and demonstration aspects. Industry, in effect, is the market for basic research. Dr. Keyworth recounted a discussion with several science ministers during his recent trip to Japan. That country has a strong base in science and technology, but its basic research lags behind that of the United States and Western Europe. The Japanese recognize that in order to maintain their leadership, they must invest heavily in basic research. In the United States, industry really provides a market for postdoctoral scientists and engineers. Industry should also assist in training, and indeed Exxon's $15 million in grants for graduate education in engineering is just the kind of support that the Administration is seeking to promote. The Committee's examination of cooperative research relationships with industry is a most important concern. The Federal Government must try to stimulate this relationship indirectly through such mechanisms as tax incentives. Dr. Keyworth concluded by reiterating his support for the Committee's work.

Committee Discussion

Dr. Malone asked Dr. Keyworth to comment on recent efforts to obtain Federal support for instrumentation at the university level. Dr. Keyworth replied that he has discussed with Dr. Paul Gray, of MIT, and others the problem of attracting people to research in academia. A number of questions were raised concerning salaries and the need to spend so much time in trying to develop grants. Another issue was instrumentation. The quality of life in academic institutions is deteriorating, and laboratory facilities and instruments are part of the problem. An interagency panel has been created to try to draw up a plan for support of instrumentation. Dr. Keyworth added that instrumentation in universities in this country is at a disgraceful level as compared with that in industry or in Western Europe. Over the past decade, with declining support for science vis-a-vis inflation, the effect has been to maintain support for the researchers rather than invest in plant and instruments. The interagency panel recently began to examine possible collaboration for FY 1983. Dr. Keyworth must now consider this in light of other priorities with the planned budget cuts for FY 1983, but he will try to fit it into the budget. It cannot, however, be addressed by trying to restore the 1960 level for capitalization of equipment. Commitment to some modest increment, however, is important.

Dr. Bennett said that he is delighted with Dr. Keyworth's commitment. So many studies have identified the need that he is gratified that the OSTP Director recognizes the problem and is trying to deal with it without commissioning further studies. He went on to note, however, that there are other problems, particularly vis-a-vis Government-industry relationships, and some conflicts with much of the legislation that has been passed, such as the 1981 tax bill. For example, there have been economic incentives for industry to give equipment to universities in return for tax writeoffs, but the tax law has accelerated the depreciation schedule for industrial equipment so that its cost can be written off in three years. So these policies, in effect, almost cancel each other out: there is little incentive for industry to give equipment to universities. OSTP might be an excellent place to try to resolve other contradictions and differences so that there can be more industrial support to universities.

Dr. Keyworth replied that much of the legislation passed is only at the first stage. The tax package will be revised yearly as the effects of the first initiatives are assessed. He stressed the importance of these tax programs to the tax and budget initiatives for the President's economic recovery program. He added that Canada has many of the same incentives that the Congress has passed. Dr. Keyworth is dealing closely with other Presidential advisors, particularly in the Office of Policy Development.

Dr. Lowe pointed out that the Government could do far more to stimulate use of Federal patents. For example, the Government currently owns 30,000 patents. Fewer than 1,500 have been licensed to industry, and NIH holds approximately 65 percent of these. Thus, there is an opportunity for industry to increase the number of licensed patents to facilitate technology transfer and commercialization. Dr. Keyworth replied that technology transfer is very important and that the President strongly endorses the changes in the patent law to facilitate the commercialization of Government-supported research. There is support, therefore, for Congressional action to ensure that grantees who hold patent rights for such inventions get them to the marketplace. Dr. Keyworth does not concur with Admiral Rickover's statement that current patent laws do not restrict the transfer into commercialization.

Dr. Keyworth praised the achievements of the United States in basic research. In the development of the transistor and recombinant DNA, we lead the world; but in commercialization of such basic research, we lag behind many Western European countries and Japan.

Dr. Hansen spoke of the Committee's work on the costs of biomedical research and particularly Federal accountability policies, which seem to stress accounting rather than the quality of the science. Dr. Keyworth replied that he is very familiar with the problems associated with OMB Circular A-21, which in his view, is just the straw that broke the camel's back. A-21 has the realistic purpose of attempting to account for Federal funds, but accountability issues should not convert to accounting issues. Rather, they should be concerned with scientific productivity and excellence. American research has a leadership role in the world, and its excellence must be maintained. Overemphasis on accounting methods can lead to mediocrity--something to be assiduously avoided.

Dr. Bondurant picked up the theme of excellence versus mediocrity, asking how excellence can be maintained in the face of continuing budget cutbacks. Dr. Keyworth emphasized that the cuts should not be linearly distributed, that excellence must be rewarded. It would be a disaster if we supported the trend toward mediocrity. Thus we must work together to define excellence in order to set priorities for determining where the dollars will go. We cannot allow our top research institutes, which are unmatched in the world, to deteriorate.

Dr. Bondurant remarked that since World War II the Congress and the President have had shifting views concerning support for intramural and extramural research. He asked how Dr. Keyworth views this matter. Dr. Keyworth replied that the United States has never had a science policy. Science is now mature and is probably in its third generation of development. Funding of basic research is principally a role of Government, but we need to analyze this role to determine a policy for support. He added that the Government understandably avoids setting a policy, because it means more dollars and a long-term commitment. He commented on the excellent track record of the Department of Energy's research program, with its wide range of basic research comparable to NSF's. And NIH, he said, has rarely been criticized for its emphasis on basic versus applied science. In his view the research agencies in general have had a good mix based on their missions. But with new budget realities, a Federal perspective may be needed.

Dr. Malone identified research manpower as an area that desperately needs a comprehensive policy. Over the past several years, there has been no Federal consensus concerning adequate support, particularly between the Department and the OMB and between the Executive Branch and the Congress. Dr. Malone pointed out that this uncertainty has wreaked havoc in the years where a lack of both funds and consistent policy has deterred excellent people from scientific careers. Dr. Keyworth agreed that the manpower issue is certainly one of the most difficult areas in which to allocate Federal support. Here again identification of priorities is essential. Linear distribution of cuts hides expanding areas of need. For example, right now there is a great shortage of Ph.D.'s in applied mathematics.

Dr. McDermott noted the emphasis on scarcity of resources and the need for priorities and asked whether Dr. Keyworth thought that technology assessments could serve the allocation process. Dr. Keyworth responded that technology assessment is a valuable tool, but one must qualify its use. Allocation of funds for basic research must be based on two critical principles: first, excellence, and then pertinence. Those are the themes, and they clearly fit into this Committee's examination of Government, university, and industry relationships in respect to resources for the Nation's health research activities.

II. DAC ACTIONS ON THE INTERIM REPORT OF THE WORKING GROUP ON COSTS OF BIOMEDICAL RESEARCH

Recommendations From the Subcommittee on Costs of Biomedical Research

William Raub, Ph.D.
Associate Director for
Extramural Research and Training
National Institutes of Health

Dr. Raub summarized the recommendations of the subcommittee as follows:

1. Fixed-Obligation Grant. (See Interim Report of the Working Group on Costs of Biomedical Research, pp. 61-79 and Table I, pp. 9-11.)

   RECOMMENDATION: That NIH develop a plan for a limited trial of the Fixed-Obligation Grant, including a basis for its evaluation.

   Details of the plan will have to be worked out, but possible elements would be these:

   - No change in present peer review or award selection processes;
   - Limitation to selected classes of awards--e.g., activity circumscribed by dollar ceiling, award mechanism, or other appropriate criteria;
   - Restrictions to interested institutions with "certified" accounting systems; and
   - Accountability limited to technical reporting except in rare cases.

2. Prior Approvals. (See Interim Report, Table IV, pp. 15-16.)

   RECOMMENDATION: That NIH consider expansion of prior approval delegations to institutions (for example, preaward costs, general-purpose equipment, and others to be identified).

3. Indirect Costs--Audit and Budget System Changes. (See Interim Report, Table III, pp. 13-14.)

RECOMMENDATION: That NIH and higher levels of the Department develop plans in two areas:

- Elimination of retrospective adjustment of indirect costs coupled with administrative simplifications, such as increased flexibility regarding carryover of unexpended direct costs.
- Redefinition of eligible indirect cost elements (e.g., eliminating some or all expenses for "departmental administration"; allowing some interest expenditures), coupled with significant reductions in administrative burden (e.g., elimination of time-and-effort reporting, and documentation of cost-sharing).

4. Modifications in Authorities and Simplification of Grant Operations. (See Interim Report, Table II, p. 12.)

RECOMMENDATION: That NIH study procedural changes--

- To increase flexibility with respect to the period of grant awards;
- To expedite review of small grants; and
- To identify prospectively those closely related projects between which cost transfers may be authorized in advance.

In addition to these formal recommendations, Dr. Raub presented to the Committee for consideration a fifth item: the proposition contained in the Interim Report (p. 4) that "Given the choice between supporting more investigators less than adequately or fewer investigators adequately, we would favor the latter." Dr. Temin had taken issue with this statement at the previous day's meeting of the subcommittee.

Committee Discussion and Action

The Committee discussion opened with the focus on Recommendation 3 regarding indirect costs. Dr. Eyzaguirre commented that the concept of carryover for unexpended direct costs from one year of the grant to the next was an excellent idea and would be very helpful to the investigators. Dr. Raub noted that this concept was coupled with the elimination of retrospective adjustment of indirect costs. Dr. Hansen said that these two were grouped together because currently 2 percent of all grants are returned to NIH as unexpended funds, which permits NIH and the individual Institutes to fund several hundred new awards each year.

Dr. Malone commented that Recommendation 3 suggested control of indirect costs, and he wondered whether the Working Group had considered the impact of this on direct costs. Namely, would direct costs increase through redefinition of indirect cost elements? Dr. Raub replied that the Working Group had not explicitly considered the impact, but that if the indirect costs were restricted, some would be treated as direct cost items. Thus, there was a need, as indicated in this recommendation, for redefinition of items under indirect costs, and that would rest with the Department.

Mr. Kirschenmann commented that redefinition of eligible indirect cost elements, if undertaken by his staff, would necessarily be widely discussed, and might lead to a change in Circular A-21. Dr. Hansen reported that a number of people she has spoken to would support the recommendation because, while there might be a problem in the first few years, the recovery rate would subsequently even out, particularly if based on good-faith negotiations.

Dr. Bennett asked whether an overestimation resulting in overpayment of a university the first year would mean that there would be no retrospective adjustment, thereby permitting the university to keep the money. Mr. Kirschenmann said that generally things equal out. Right now the Department allows the use of a fixed rate with carry-forward. The carry-forward is an adjustment for the previous year's over- or underestimate of the rate. Mr. Kirschenmann referred to Dr. Hansen's concern that the Government often uses "scale" numbers for rates, but said he had no problem with using new numbers. Dr. Wilson pointed out that the concept of a fixed rate and carry-forward has to do with the determination of the rates, not the payment of them, and that it should be made clear that the subcommittee's recommendation is analogous to the present NSF method of payment, in which there are no retrospective adjustments of indirect costs by the agency within the grant period. However, she urged great caution in reviewing indirect cost elements, particularly in terms of the impact on universities. There is no easy solution, and if changes were made arbitrarily great damage could be done to the research capacity of the Nation.

Mr. Hutt asked how long it would take to complete a study on redefinition of indirect cost elements. Dr. Wilson thought it would take up to a year and added that a committee of relevant Government, university, and OMB people would be needed to design the study. Mr. Kirschenmann felt that a year would be too long, that we must move very quickly, particularly with the budgetary constraints. In his view, he and his office could at least prepare a proposal for review by a group or forum such as Dr. Wilson suggested, but we have to move quickly and get some agreement as soon as possible; otherwise, we will lose the initiative. It is essential that something be done, especially in light of the continued cutbacks in Federal funding projected for FY 1982, '83, and beyond.

Mr. Dummer asked whether this would not require some revision in A-21 and thus reopen that entire process. Mr. Kirschenmann noted that there are ongoing discussions about A-21, but he believes that given the budget situation, some agreement might be reached quickly without reopening the whole matter of the circular. Dr. Wilson acknowledged the importance of timing, but cautioned against preparing something hastily without appropriate consultation. Mr. Dummer urged that sufficient time be allowed for input by faculty and university administrators, especially since consultation here would be essential for implementation of any proposal. Dr. Temin commented that Mr. Kirschenmann appears to be suggesting the preparation of a plan to be reviewed and acted upon, rather than the creation of a committee to develop a plan.

Dr. Bennett expressed concern about the recommendations and ensuing discussion. He said that from the investigators' perspective, the pot of money for direct costs shrinks as indirect costs increase. They feel that they are being penalized by indirect cost increases. If one changes or limits indirect costs, they will simply fall more on the principal investigator and direct costs. In one way or other, the universities cannot afford to support the research environment except by recouping funds. Indeed, Dr. Bennett believes that the current NIH model is excellent, and he has been urging the Defense and Energy Departments to consider using it. Representatives from both Departments are now talking to Dr. Raub and Mr. Bernard about our process. Dr. Bennett urged caution in trying to change the present NIH model, stating that we need more thought here and perhaps small-scale trials rather than some systemwide implementation that may place greater stress on the universities and force them to underrecover indirect costs when no substitute funds are available.

Dr. Wilson responded that the subcommittee was not recommending a fundamental change. In terms of administrative flexibility, there would still be an annual readjustment of indirect cost rates, and that would make NIH consistent with the other Federal agencies. Dr. Porter said that this is a serious matter for the principal investigator and he strongly supports the recommendation. He agrees that the present trend cannot be continued, and that there must be some system under which indirect costs will be constrained along with direct costs in the difficult budget times ahead.

Dr. Eyzaguirre strongly endorsed Dr. Porter's remarks, noting that the principal investigator must be aware that all systems share in the budgetary constraints. Mr. Hutt wondered where the extra dollars would come from if indirect costs were constrained as budgets go down. Dr. Wilson replied that basically they would come from reducing services for the researchers, both in number and quality. Dr. Temin commented that more and more services would be added onto the direct costs column, which would then go through the peer review system, perhaps a more appropriate mechanism. Another element is the pressure of Government regulations that are factored into the indirect cost rate and have increased enormously the administrative costs for the institutions. He proposed a tradeoff in reducing regulations: indirect costs would decline with the lower regulatory burden.

Dr. Bondurant commented that it is important to recognize the significant differences between public and private institutions in ability to absorb indirect costs. Experiences in one sector may not be valid for the other. Dr. Temin noted that the Committee clearly endorses Recommendation 2 on prior approvals and Recommendation 4 on modifications in authorities and simplification of grant operations. Dr. Malone asked whether there were any objections to these two recommendations, and there were none. Further, Dr. Malone said there seemed to be consensus to develop a proposal for implementation of Recommendation 3, but that clearly it should be brought back to the Committee or the Working Group for review. There was no objection to that approach.

Regarding Recommendation 3, however, Dr. Wilson suggested that a third item (c) be added to reflect the subcommittee's strong reservations concerning the imposition of a uniform indirect cost rate, and there was support for this.

Dr. Temin noted that Recommendation 1, for the Fixed-Obligation Grant, called for an evaluation, and he urged that it be qualitative rather than quantitative. Dr. Raub noted that it had been suggested that some evaluation would be worthwhile, but he recognized the issues that Dr. Temin brought up and felt that they could be accommodated.

Mr. Fundingsland remarked that the principal investigator should love the Fixed-Obligation Grant, looking at it, in effect, as a blank check for research funds with very little fiscal accounting. But with the elimination of financial accountability, there must be some way to verify the use of the taxpayers' funds. Thus, a record of costs must be kept, even with this type of grant. He felt that it might be more meaningful for study sections to look not only at direct costs but also at total costs because universities vary so greatly in the types of costs that are categorized as direct or indirect. Hence, total costs provide a better basis for comparison. He added that the high degree of stress between the Government and the university regarding accountability argued for an experiment to see whether another model might be appropriate. With increased focus on budget cutting and Congressional oversight, there will be increased scrutiny of the disbursal of Federal funds by the Congress.

Dr. Wu returned to the theme of indirect costs and the concern of the principal investigators. Using the data given in K. T. Brown's article "Indirect Costs on Federally Supported Research," she noted that over the past 13 years, direct costs have risen 35 percent but indirect costs have jumped 250 percent in the same period. She suggested the use of incentives to hold down costs. Perhaps NIH could give bonuses or awards to those universities that reduce costs or at least have a more efficient system in place. Under the direct cost of her grant, she has to pay for her graduate students. Now she supports six, so her grant is reduced, in effect, by $96,000. Perhaps, she said, consideration might be given to a uniform base for indirect costs with variations to allow for differences in location, private or public support, age of buildings and the like. But indirect costs must be continually examined, with a view to holding down their escalation.

Dr. Wilson explained that the Fixed-Obligation Grant is not a mechanism to deal with indirect costs, but an attempt to create one of several models for the administration of grants that would give the local institution more autonomy in use of the funds, with fewer administrative and regulatory requirements from the Federal level. Mr. Dummer asked, if Dr. Wilson would favor adopting the Fixed-Obligation Grant for those reasons alone if in practice it resulted in no reduction in costs. Yes, Dr. Wilson replied, we are losing scientific productivity because of regulations and numerous auditing requirements. She added that institutions would still need to handle cost data and the Government would audit the general system; but this would be better than the present grant-by-grant approach. What we are doing, in effect, is exploring a different paradigm. A lot of our problems have come from adopting the cost reimbursement basis without question. Dr. Malone commented that there seemed to be a consensus that the proposed trial for the Fixed-Obligation Grant should proceed. This was adopted without objection.

Dr. Temin referred to a statement on page 4 of the interim report: "Given the choice between supporting more investigators less than adequately or fewer investigators adequately, we would favor the latter." Dr. Temin disagreed with that position. Dr. Eyzaguirre agreed with Dr. Temin, noting that many investigators have multiple grants and that it would be better to spread the funds over more investigators. Dr. Raub indicated that there are approximately 1.1 project grants per NIH investigator and that there really is no problem here. Dr. Bondurant asked whether the Working Group had ever considered examining direct costs as it had indirect costs and whether the Working

Group's silence on this matter was an indication that it believed direct costs were appropriate. Dr. Raub responded that, indeed, the group had assumed that direct costs were not a major problem. Dr. Temin said the Working Group believed that study section review of direct costs provides adequate scrutiny. Thus, the Working Group in effect is reaffirming the present system of direct cost examination.

Dr. Temin pointed to the need for continuing education about indirect costs for all parties. Mr. Kirschenmann added that the Working Group had not looked at the larger picture, which was too difficult a mandate, but had appropriately fixed on those elements on which it could make sensible recommendations. He mentioned his reservations, as expressed by Mr. Fundingsland, on the Fixed-Obligation Grant, but believed the concept was worth a trial.

Dr. Malone noted that, having adopted the four recommendations for action, the Committee would be kept informed of their implementation. He believed the Committee had carried out over the past year and a half an outstanding examination of one of the most difficult areas in Government-university relationships--one that has stimulated continuing controversy for the past 25 years.

Second Day: Afternoon Session

III. DAC ACTIONS ON THE INTERIM REPORT OF THE WORKING GROUP ON COOPERATIVE RESEARCH RELATIONSHIPS WITH INDUSTRY

Introduction

Dr. Bennett opened by noting that the afternoon session would be based on the draft outline for patent policy guidelines that had appeared in the Interim Report of the Working Group on Cooperative Research Relationships With Industry (pp. 8-17). (See Attachment 4 for the outline as revised by the DAC subcommittee.) He acknowledged the excellent cooperation of the Working Group and the superb staff support that had resulted in a number of steps to alert the academic community regarding OMB Bulletin 81-22, implementing P.L. 96-517, "The Patent and Trademark Amendments Act of 1980." (See Attachment 5.) A letter over Dr. Malone's signature had prompted a number of universities to send comments on the directive to the OMB. Dr. Bennett cited the book of letters prepared for the meeting, Compilation of Comments to the Office of Management and Budget on OMB Bulletin 81-22, Implementation of Public Law 96-517, "The Patent and Trademark Amendments of 1980." (See Attachment 6 for preface to the book and analysis of the letters.) He added that the OMB has been most cooperative, particularly Fred H. Dietrich, Associate Administrator, Office of Federal Procurement Policy, who was responsible for the OMB directive and had participated in yesterday's subcommittee review. Dr. Bennett then reviewed the general recommendations of the Working Group that had been approved at the subcommittee meeting.

RECOMMENDATIONS: That--

- NIH require all institutions receiving funds to have a patent policy (see Section V of draft outline);

- NIH waive or elect not to exercise procedural and other discretionary requirements not mandated by law as regulation, and not develop procedures unique to NIH unless they are considered essential in meeting the mandated responsibility (see Section V of draft outline);
- NIH consider developing a policy on treatment of proprietary information in concert with constituents and in light of the need to reconcile implementation of the new patent law with departmental procedures for making grants to profit-makers (see Section VI A 5 of draft outline);
- NIH convene a meeting of study section chairmen at an appropriate time to discuss handling of proprietary information (see Section VI A 5 of draft outline);
- NIH include in its guidance to grantees a glossary of terms and a "mini-primer" on the patenting process, from the point of discovery through disclosure and reporting requirements (see Sections V and VI A 3 and 4 of draft outline); and
- NIH make available to grantees examples of existing contractual agreements, which may provide insight concerning time-oriented provisions.

Two additional recommendations had been modified by the subcommittee: That--

- NIH consider initiating a limited, preliminary study of issues surrounding commingled funds; and
- NIH request the OMB to insert a "de minimis" provision in the section of the regulations dealing with commingled funds, in order to exempt from procedural requirements research receiving only marginal Government support.

However, these recommendations were changed as follows, in view of comments by Mr. Dietrich (described below in respect to Mr. Hutt's presentation).

RECOMMENDATIONS:

- That NIH review OMB cost-accounting principles, in conjunction with HHS auditing procedures, to determine whether they are applicable to the issue of commingled funds or whether further study is required.
- That NIH include in its guidance both the relevant portions of regulations (45 CFR 8.2(d)) that allow waiver of rights when its interest is minor and examples of situations where cost-accounting principles allow a clear assignment of title.

Dr. Bennett then relayed some comments by Mr. Dietrich regarding the status of OMB regulations:

- The regulations are currently being revised. October is the target date for release of a penultimate draft of the OMB Bulletin, which will be reviewed by agencies prior to final promulgation.

- Mr. Dietrich agreed to meet with NIH staff to discuss areas of concern in the draft.

- The OMB will attempt to convene a group of agency representatives and affected parties to address concerns raised regarding the alternate language in the patent rights clause.

- The OMB will seek to develop substantive and procedural criteria for the exercise of march-in rights. It is unlikely, however, that these will be ready for the next issuance of the regulations.

- It appears that the Department of Commerce will be designated as lead agency. That department is viewed as having cross-cutting responsibilities and, within its charter, a basic charge to commercialize technology. Mr. Dietrich emphasized, however, that the lead agency will not issue regulations; this authority will be reserved for the OMB.

Dr. Bennett announced that various members of the Working Group would present for DAC review issues relating to the patent guidance.

When the Institution Retains Title

Allocation of Patent Rights

Charles U. Lowe, M.D.
Acting Associate Director for
  Medical Applications of Research
National Institutes of Health

Dr. Lowe summarized yesterday's review on the allocation of patent rights as follows:

- The Working Group discussed whether the NIH guidance should use "transfer of title, retention of title, election of title," or other terms to describe the allocation of patent rights to either the Government or the contractor. There was general consensus that the intent, as well as the language, of the new law makes clear that title will automatically reside with the contractor, unless very specific conditions obtain.

- The NIH guidance has been revised (see Section V--Policy) to reflect the general policy of NIH to encourage institutions to elect title.

- As recommended by the Working Group, the guidance has also been revised to make clear to institutions that they must exercise the option to elect title within a specified time period, or they will lose certain rights.

- The Working Group noted that the draft NIH guidance dealing with allocation of rights seeks to ensure that no unnecessary administrative burdens will be placed on institutions.

- Consistent with Working Group recommendations, the draft guidance is being revised to indicate that existing NIH institutional patent agreements will terminate upon the effective date of the OMB Bulletin. The guidance will note, however, that this action will not abrogate licensing contracts entered into under existing IPAs.

Effect on Allocation of Patent Rights When Federal Funds Are Commingled With Industrial Funds

Peter Barton Hutt
Attorney at Law
Covington & Burling

Mr. Hutt summarized the previous day's proceedings as reaching agreement on the following issues:

- The Working Group has been concerned that any patentable invention resulting from research funded in whole or in part by the Government is subject to the requirements of the new law and regulations.

- The results of commingling might act as a disincentive to commercial support of university research--a situation antithetical to the intent of the new patent law.

- Because of its concerns, the Working Group had previously recommended that NIH (1) consider initiating a limited preliminary study of issues surrounding commingling and (2) request OMB to insert "de minimis" wording in its regulations in order to exempt from procedural requirements research receiving only marginal Government support.

- Insight provided by Mr. Dietrich, Office of Federal Procurement Policy, OMB, has led the Working Group to alter its recommendations. Mr. Dietrich indicated that--

  --The commingling issue can largely be addressed by HHS auditing procedures used in conjunction with OMB cost-accounting principles.

  --OMB would be guided in commingling decisions largely by indirect and direct cost distinctions. When the Government provides direct costs, such as salary support, the Government obtains rights to any resulting patents. Previous Government funding for equipment or facilities--in the nature of indirect costs--does not give the Government any rights to the resulting patents unless the funding agreements contains a specific provision retaining such rights.

--With respect to commingling of ideas, Mr. Dietrich suggested that the Government would have no rights in the resulting patents unless some subterfuge was involved. The investigator's intent would clearly be important, and suspect actions would be subject to audit.

--According to Mr. Dietrich, an OMB circular is an inappropriate place to discuss such accounting considerations, but an NIH circular would be an appropriate place.

- In light of Mr. Dietrich's comments, the Working Group has suggested that NIH address the commingling issue in its guidance to grantees, and provide examples of various cooperative research situations that would or would not involve commingling.

- In addition, the Working Group suggests that NIH continue to use HHS regulations (45 CFR 8.2(d)), through which the Department can waive its rights (except for royalty-free rights) to inventions developed under its support.

- The Working Group also suggests that NIH review OMB cost-accounting principles in conjunction with HHS auditing procedures, to determine whether further clarification or a study is required regarding commingled funds.

Mr. Hutt stated that the discussion with Mr. Dietrich had been especially helpful, for they had gone over several examples to guide the institutions on this matter. Mr. Hutt reviewed these examples, which the Working Group had suggested should be included in the guidance. The examples were as follows:

- If NIH provides funds for a laboratory building and 10 years later industry supports research in that building, the Government would have no patent rights in inventions discovered through the industrial research.

- If the Government funds the purchase of laboratory equipment that is used in industrial research after completion of the original project, the Government has no patent rights in inventions discovered through the industrial research.

- If a professor on Government funds and a professor on industrial funds discuss research issues and the former professor suggests an idea to the latter, and the industrially funded professor develops an invention, again the Government will have no patent rights in that invention, unless there had been outright fraud or appropriation of the idea from the Government-sponsored researcher.

Mr. Hutt went on with another example:

- If a professor is receiving 50 percent Government funds and 50 percent industrial funds and his research projects are completely different, the Government has no patent rights to the inventions developed under the industrial funds. Concerning closely related projects where there is joint funding, again there would be no question, provided the professor does the research in the morning on Government funds and in the afternoon on industrial funds and there is strict accounting for those funds.

Finally, there was the issue of sequential funding, which Dr. McDermott had raised:

- If an investigator were funded by NIH for three years and then by industry for the next three years, and if the invention were developed in the latter period, the Government would have no patent rights in that invention. Only if the invention had been brought to conception during the first three years would the Government have patent rights.

Mr. Hutt commented that these examples and Mr. Dietrich's response are very reassuring. The industrial invention can be differentiated and corporate sponsors protected from a possible loss of their patent rights. Accordingly, he felt that there is no need for a study.

Committee Discussion

Dr. Temin asked whether another accounting system would be required, especially in the case of the professor working in the morning on Government funds and in the afternoon on industrial funds. Mr. Hutt replied that time accounting would be required, but that that should not be too difficult. Dr. Andrews pointed out that lab notebooks would then be the key for detailing the time; there would have to be some system.

Mr. Fundingsland remarked that the law had been passed to encourage commercialization, but the question here became how to split the royalties between the university and industry. Mr. Hutt noted that, at least for purposes of the Government, the Government has a royalty-free license; and he added that a royalty-free license could have enormous impact for a drug covered by Medicare or Medicaid. Mr. Kirschenmann wondered whether the burden of proof would be on the university when Government funds were involved and it is not clear on which funds the invention was developed. Mr. Hutt responded that if the investigator does not keep careful records, joint funding would be presumed and the Government would obtain patent rights.

Dr. Raub commented that almost any example cited in the guidelines could be misinterpreted. Mr. Hutt agreed, but thought these were excellent illustrations that would go a long way to easing industrial and university concerns. Mr. Fundingsland pointed out the problem of investigators consulting with industry and how rights would be allocated in such circumstances. Mr. Hutt agreed that it would be a problem best left for the universities to solve.

Dr. Bennett concluded by noting that in his experience over the past three or four months, the universities clearly had not known about the pending regulations, but neither had industry. Considerably more attention would have to be given to these issues by the Government, industry, and universities over the next several years.

Administration of Patent Rights Clause

Fredrick N. Andrews, Ph.D.
Vice President
Purdue Research Foundation
Purdue University

Dr. Andrews explained that his report concerned the following sections of the patent guidelines as outlined: VI. Implementation, A. When the Institution Retains Title to a Patent: 1. Allocation of Rights, and 2. Administration of Patent Rights Clause. (See Outline of Patent Guidelines, Attachment 4.) Dr. Andrews opened by noting that the Working Group was not wholly satisfied with either the law or the OMB regulations, but that both were furthering a uniform patent policy, which is an important national goal. Other bills have been introduced in the Congress that will modify the law and extend it, and we can expect a number of changes over the next several years.

Dr. Andrews noted that one of the key recommendations of the Working Group for purposes of the patent guidelines was that all universities must have a patent policy. He emphasized that the guidelines were very general in this respect, that there were no detailed mandates concerning royalties, etc. Dr. Temin urged that a patent policy not be required for all institutions. Dr. Bennett commented that this provision was recommended by the Working Group in furtherance of the statute and the OMB directive, because the intent here is that inventions be moved to patenting as quickly as possible for purposes of commercialization. Dr. Temin replied that this is sound for institutions like his university, but that many small colleges should not be required to prepare a patent policy, since it is unlikely that they will have many inventions. Dr. Bennett commented that such a policy is part of an institution's obligation in accepting Federal funds, and that the new law and the OMB directive introduce a statutory basis for institutional compliance.

Dr. Andrews pointed out that the patent guidelines, in effect, incorporate the provisions of the institutional patent agreements and that the new statute will rationalize the structure for all NIH grantees and contractors. The universities need this to have a sensible procedure for the patenting of new inventions. Dr. Bondurant pointed out that the OMB directive requires written agreements between the university and its employees regarding the reporting of inventions for purposes of patenting. The universities will need something on the books in any event. Dr. Lowe went on to point out that, under the NIH grant program, inventions developed with grant support must be reported.

Dr. Wilson agreed with Dr. Temin that many colleges and universities do not conduct the kinds of research that are likely to lead to inventions--in behavioral and social sciences for example--and therefore should not be required to have a patent policy. For example, HHS has approximately 95 institutional patent agreements, but Dr. Malone's directive went to all 1,200 institutions receiving NIH support. Surely several hundred of these institutions should not be required to have a patent policy. Requirements that are "good advice" but not required by law should not be imposed. Mr. Hutt noted that perhaps the guidance might include a statement that any institution that has not achieved inventions from Government-supported research and is not likely to do so need not develop a patent policy. However, Dr. Bondurant disagreed, pointing out that the history of the institution may be irrelevant in view of the shift of Federal policy to stimulate the development and patenting of inventions and commercialization.

The Working Group had also recommended that institutions prepare and provide NIH with a development plan if a patent is to be licensed. The subcommittee, however, indicated that such a plan (particularly specifics regarding royalties) would be viewed negatively by universities, as well as by commercial firms that might wish to engage in cooperative research with them. The subcommittee rejected the suggestion, and the Committee concurred.

Dr. Bennett added that the minutes can reflect the different views concerning the requirements for patent policies at universities, and NIH can take these views into account in its consideration of patent guidance.

Reporting Requirements for Inventions; Invention Disclosure and Filing of Patent Applications; Publication Restrictions

Stuart Bondurant, M.D.
Dean, School of Medicine
University of North Carolina

Dr. Bondurant reported on the previous day's subcommittee meeting. The group had discussed part 5b(1)(vi) of the OMB Bulletin, which allows agencies to use alternate language requiring submission of invention disclosures three months prior to their submission for publication. Universities have voiced exceptionally strong opposition to the OMB concerning this "prenotification" provision, and the NIH guidance has been revised to make it perfectly clear that NIH will not exercise this option. Moreover, the Department of Health and Human Services has recommended to the OMB that use of the alternate language be made subject to the "exceptional circumstances" reporting to the Comptroller General as required in the regulations.

Mr. Dietrich had indicated to the group that the "alternate clause" issue is particularly knotty. At present, the OMB is considering several options, including having universities submit their manuscripts to the Government at the time they are submitted for publication. The Government would decide at that point whether there was a need to withhold publication. Working Group members had commented that this option would give even greater authority to agencies. Moreover, scientific journals would probably not accept a manuscript if there were any possibility that the Government could delay its - publication. Mr. Dietrich had indicated that the OMB would attempt to convene a group of agency representatives and affected parties to address the alternate provision issue.

RECOMMENDATION: That NIH revise the draft guidance to eliminate any reporting requirement that was neither mandated by law or regulation nor viewed as absolutely essential.

Dr. Temin asked how one would determine whether an invention is patentable. Dr. Bondurant replied that the OMB Bulletin defines "subject invention" as an invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement. He said it would be the responsibility of the principal investigator to make that determination. He added that the OMB, according to Mr. Dietrich, does not believe any sharpening of that definition is in order, because it will have to be more generally discussed and developed in terms of guidance from the agencies and the universities.

Dr. Temin said he interpreted the statute to mean that conceivably every recombinant DNA clone is patentable, and that if applications were always submitted, the system would be quickly swamped. Dr. Bondurant responded that in practice it will largely be left to the investigator and the universities to determine which inventions should be pursued for patentability. He acknowledged that this was not entirely consistent with the law, but this is what would probably occur. He added that what is really needed is an operational definition in the NIH patent guidelines, and the Working Group has suggested that NIH develop such a definition.

Mr. Hutt commented that Dr. Bondurant is right, in that the statute clearly says all inventions must be patented and there are no exceptions. He stressed the importance of trying to develop an operational definition for use by NIH grantees and contractors. Dr. Raub pointed out that there has not been a flood of inventions from chemistry, a discipline where systems for patenting have been in place, and that the statute would have the same effect in biology. Dr. Lowe noted, however, that the NIH grant instrument now requires the reporting of inventions, so the problem cannot be ignored. Dr. Bondurant remarked that the Working Group had spent three meetings on this issue but could not develop an operational definition. Clearly, additional work will have to be done by NIH.

Protection of Proprietary (Trade Secret and Commercial) Information

Peter Barton Hutt
Attorney at Law
Covington & Burling

In the research community, Mr. Hutt began, protection of trade secret and commercial information is uniformly misunderstood and feared, though relatively clear. Two statutes are involved: the General Federal Reports Act of 1864 (18 U.S.C. 1905) and the Freedom of Information Act of 1966. The earlier act stipulates that any Government official or special employee who obtains trade secret or confidential commercial information and makes it available to those outside the Government is subject to criminal penalties. The Freedom of Information Act provides the presumption of disclosure with limited exemptions, the fourth exemption repeating the 1864 Act.

Mr. Hutt then discussed the 1974 Washington Research Project case as germane to the issue. This case involved a request that NIH release the contents of a funded grant application which NIH considered proprietary. In court, NIH said the information was only of academic value. The court concluded that the material had to be released because it was not believed to be of commercial value. According to Mr. Hutt, this ruling has been incorrectly interpreted to mean that all funded research grants are public. He stressed, however, that the law does not distinguish between funded and unfunded studies. The legal basis for distinction is whether there is information of commercial value to be protected.

Mr. Hutt also reviewed a more recent case involving the Chrysler Corporation. Here the Supreme Court stated that the 1864 criminal statute covers all Government employees and prohibits the release of commercial information. From Mr. Hutt's perspective, the impact of the 1980 patent law is to make no legal distinction between funded or unfunded grants and to mandate commercialization of federally funded discoveries. Accordingly, NIH must determine whether confidential information is commercially valuable and thus whether it is or is not a trade secret. If NIH determines it is confidential and a commercially valuable trade secret, it must be protected from disclosure. Mr. Hutt noted that when the Recombinant DNA Advisory Committee had initially declined to handle confidential commercial material, industry would not submit proposals containing proprietary information. Hence, the Committee changed its procedures and now does protect the information. NIH must develop analogous procedures for its study sections.

Mr. Hutt stated that the potential impact of the new patent law on the treatment of proprietary information with respect to both funded and unfunded grant applications has led the Working Group to recommend the following--

RECOMMENDATIONS:

- That NIH consider developing a policy on treatment of trade secret and commercial information in concert with constituents.

- That NIH convene the study section chairmen to discuss the handling of trade secret and commercial information.

Dr. Temin asked whether the NIH administrative burden might not be reduced if study sections did not have to consider confidentiality, adding that NIH could resolve this issue with the principal investigator at the time a Freedom of Information request is received. Mr. Hutt felt this was not a solution because there are time constraints on responses to Freedom of Information Act requests. Generally, there is a ten-day limit.

Dr. Bennett noted that in view of the Working Group's considerations as presented by Mr. Hutt, NIH must proceed to develop a system. Dr. Temin commented that this would become a huge problem in the area of recombinant DNA, where every discovery may be patentable. Mr. Hutt responded that other agencies, such as EPA and FDA, have been able to cope and that he believes NIH could do as well. Dr. Bondurant suggested that another option might be to amend the Freedom of Information Act to exclude research grant proposals or awards. Mr. Hutt noted, however, that the concept of "trade secrets" covers all information. It is therefore important for NIH to have procedures for study section protection, irrespective of an amendment to the Freedom of Information Act. Dr. Bennett agreed that this is necessary because NIH will soon be handling grant requests from profit-making organizations.

March-In Rights

Fredrick N. Andrews, Ph.D.
Vice President
Purdue Research Foundation
Purdue University

Dr. Andrews continued the report on the subcommittee meeting of the previous day. Some members of the Working Group had felt that the OMB Bulletin did not adequately address march-in rights. Mr. Dietrich had noted, however, that the OMB will be developing criteria in this regard for issuance at a later date.

RECOMMENDATION: That NIH/HHS begin to develop its own procedures for the exercise of march-in rights.

In this regard, it should be noted that the Department of Health and Human Services has indicated to the OMB that (1) it views march-in requirements as unnecessarily burdensome and (2) recommends omitting many of the details contained in the Bulletin and keeping the procedures as informal as possible.

RECOMMENDATION: That NIH attempt to clarify what is meant by "reasonable time" with respect to university efforts to commercialize an invention.

As recommended by the Working Group, the NIH draft guidance has been revised to indicate that NIH will view as reasonable those times set out in licensing agreements by the parties involved.

When the Institution Does Not Retain Title

When NIH Acquires Title

George H. Dummer
Director
Office of Sponsored Programs
Massachusetts Institute of Technology

Mr. Dummer reported that the subcommittee had spent a good deal of time on the circumstances that pertain when the institution relinquishes title. Because of a number of questions about how NIH acquires title, that aspect of the guidance, section (VI)(b)--Implementation--has been completely rewritten. The revised section deals with the three circumstances under which NIH acquires the title: (1) when the institution elects not to retain title, (2) when the institution forfeits title, and (3) when funding agreements provide NIH with the title. (See Attachment 4 for NIH guidance.) Mr. Dummer believes that this section as rewritten goes a long way toward clarifying the circumstances in which NIH may acquire title.

Conclusions

Dr. Bennett stated that the Working Group had narrowed its mandate to deal with the impact of the new patent law on NIH programs. He was pleased with the progress and particularly with the cooperativeness of the OMB and of Mr. Dietrich, who had assisted at the subcommittee meeting in sharpening up the guidance for NIH and clarifying a number of ambiguities. Dr. Bennett stressed the importance of this matter for Government-university-industry relationships. NIH must continue in its leadership role and perhaps may want to consider convening conferences or the like to continue the dialog for the universities. Here we will need a good deal of advice. Perhaps NIH, because it is so heavily involved in this area, might wish to consider supporting meetings through outside bodies. Mr. Hutt remarked that NIH may not have to act here, as there are so many meetings going on already. At the meeting yesterday with Mr. Dietrich, he added, there seemed to be a consensus that the Commerce Department should be the lead agency for administering the new Federal patent policy, as suggested in many comments to the OMB on the Bulletin.

Dr. Malone asked whether there were objections to adopting the recommendations of the Working Group. There were none, and the report was adopted. Dr. Malone announced that there would be Committee reports summarizing and including the actions by this two-day meeting, with distribution among NIH advisory bodies and others with administrative interest in NIH programs.

Dr. Malone noted that this was the last meeting for Mr. Hutt and Drs. Bennett, Bondurant, and Wu. In addition, Dr. Bennis and Mrs. Wexler, who had been unable to attend the meeting, would also be leaving. He expressed appreciation for the work of the Committee, and especially for that of the retiring members.

Dr. Malone added that Dr. Perpich would be leaving NIH in mid-December to become Corporate Vice-President for Planning and Administration of a new firm engaging in recombinant DNA technology. He briefly reviewed Dr. Perpich's contributions to the NIH policy on recombinant DNA research and the health research strategies for Dr. Fredrickson and the Institute Directors, as well as his staff support for the DAC. There being no other business, the meeting was adjourned at 3:55 p.m.

Respectfully submitted,

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November 18, 1981
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